Nephrol Dial Transplant (2011) 26: 196–205
doi: 10.1093/ndt/gfq333
Advance Access publication 22 June 2010

Vegetarian supplemented low-protein diets. A safe option for pregnant CKD patients: report of 12 pregnancies in 11 patients

Giorgina B. Piccoli[1], Rossella Attini[2], Elena Vasario[2], Pietro Gaglioti[2], Ettore Piccoli[2], Valentina Consiglio[1], Chiara Deagostini[1], Manuela Oberto[2] and Tullia Todros[2]

[1]SS Nefrologia, Department of Clinical and Biological Sciences, ASOU San Luigi, University of Torino, Italy and [2]Materno-Foetal Unit, ASOU OIRM S. Anna Hospital, University of Torino, Orbassano, Turin, Italy

Correspondence and offprint requests to: Giorgina B. Piccoli; E-mail: gbpiccoli@yahoo.it

Abstract

Background. Pregnancy in CKD is an increasing challenge, considering also the paucity of therapeutic tools available in pregnant women. While theoretically interesting, the experience with low protein diets in pregnancy is limited. Aim of this feasibility study is to review our experience with supplemented vegetarian low protein diets in pregnancy, as a "rescue treatment" for severe CKD and/or proteinuria.

Methods. Data were gathered prospectively. Diet schema: proteins: 0.6-0.7 g/Kg/day, amino and chetoacid supplementation, 1-3 free meals/week. Compliance, side effects, biochemical data recorded at each visit (at least twice monthly).

Results. Between January 2000 and February 2010, out of 168 pregnancies referred, 12 were managed by the diet (11 patients; median age 33, range 20-38). One pregnancy was terminated (patient's choice); the other 10 patients delivered 11 healthy babies. At referral, 2 patients were in stage 4 CKD, 4 in stage 3, 4 had nephrotic proteinuria (3.6-6.3 g/day). One patient doubled serum creatinine; none needed renal replacement therapy within 6 months from delivery. No patient complained of side effects, nor developed hyperkalemia or hypercalcaemia. Two babies from mothers in CKD stage 4 were small for gestational age; 9/11 were delivered by caesarean section (median gestational age 33 weeks: range 28-37; birth weight 935-2620 g) within a policy of delivery in the presence of foetal growth impairment and/or worsening of proteinuria, GFR, hypertension or foetal conditions. All babies are well, 1 month, 7.5 years from delivery.

Conclusion. Our report suggests considering vegetarian diets as an additional tool in the management of pregnant CKD patients.

Keywords: CKD; low-protein diet; pregnancy; supplemented diets; vegetarian

Introduction

Pregnancy is a well-known challenge in patients affected by chronic kidney disease (CKD) [1–3].

Pregnant CKD patients have a higher risk of developing pregnancy-induced hypertension and pre-eclampsia. Autoimmune diseases may experience severe flare-ups in pregnancy and puerperium [1–5]. Children born to CKD mothers have a higher risk of being small for gestational age (SGA) or premature [1–6]. The medical literature is heterogeneous and often hard to compare, but the risks of neonatal and perinatal death, and of long-term sequelae of prematurity, are believed to increase in parallel to the worsening of CKD [6–9]. In addition to the short-term challenges of CKD for the mother and offspring, the long-term effects of hyperfiltration on the progression of kidney disease are not yet clear [6–10].

Low-protein diets are important tools to slow CKD progression, at least in selected patients. Even if the quantification of their effects on the progression of renal failure is still a matter of debate, their positive effects on metabolic disorders and their clinical consequences have been more clearly established [11–14]. Vegetarian diets supplemented with amino acids and keto-acids are considered equal or superior to conventional low-protein diets, after adjustment for compliance and for a different selection of patients who choose such a demanding dietary regimen [15–18].

The main goal of low-protein diets is to reduce hyperfiltration, consequently slowing the progression of CKD. Therefore, as pregnancy induces hyperfiltration, low-protein diets can theoretically play an important role in pregnant CKD patients [6–10]. However, it is feared that low-protein diets represent a materno-fetal conflict, as a high protein intake is often counselled in pregnancy. Nevertheless, the ideal protein intake in pregnancy has not yet been assessed [19–21]. The present trend in the overall population of pregnant women is to avoid ex-

cessive protein intake, counterbalancing the older 'cultural' habit of high-protein diets. Dietary protein supplements were often employed in previous decades following cultural and marketing pressures rather than evidence-based criteria [22,23]. Thus, there is a wide experience of protein supplements in pregnancy, and no report on their toxic or teratogenic effects was available at the time of our study.

In contrast, little is known about low-protein diets in pregnant women with CKD. At the time of the present study, no study on vegetarian diets supplemented with amino acids and keto-analogues in pregnancy was retrieved from the Medline database.

The aim of our study was to report on the feasibility of the diet and on results obtained in a series of 12 pregnancies in 11 patients affected by severe kidney impairment and/or nephrotic proteinuria, managed, as a 'rescue treatment', with an original regimen of supplemented low-protein vegetarian diets.

Our diet is derived from an empirical compromise between the goal of reducing hyperfiltration and the acknowledgement of the increased metabolic needs of pregnancy. Thus, we chose an average 0.7 g/kg/day of protein and increased the supplementation throughout pregnancy. This choice was balanced against two major concerns: the use of low-protein diets and the use of dietary supplements.

Our report on 12 pregnancies in 11 CKD women managed with this diet schema is, to our knowledge, the first one on supplemented low-protein diets in pregnant CKD patients.

Materials and methods

Definitions employed

CKD was defined according to the Kidney Disease Outcomes Quality Initiative (K-DOQI) guidelines [24]. The baseline serum creatinine and proteinuria were available in nine of 12 cases. Throughout pregnancy, glomerular filtration rate (GFR) and proteinuria were assessed by 24-h urine collections.

Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, or anti-hypertensive therapy. A newborn was defined as SGA when the birth weight was below the 10th centile according to Italian birth weight references [25]. Intrauterine growth restriction (IUGR) was defined as fetal growth impairment, based on a flattening of the fetal growth curve or on an abdominal curve below the 10th centile assessed by repeated ultrasound exams with umbilical Doppler anomalies [25]. Pre-term delivery was defined as delivery before 37 completed weeks of gestational age [26].

Apgar scores were routinely recorded at 1 and 5 min by the neonatologists (according to the classic 0–10 score, for evaluating newborn vitality, taking into account skin colour, pulse rate, tendon reflex, muscle tone and breathing).

Information on the babies was obtained either at the last clinical controls or in phone interviews.

Study setting and control policy

The study was performed in the Materno-Foetal Medicine Unit of Sant'Anna University Hospital, Turin, Italy. From 2000, all patients with CKD were followed by the same obstetric and nephrological team. Data were gathered prospectively from the start of the activity. In the period 1 January 2000–28 February 2010, 168 pregnancies in CKD patients were referred. In keeping with the wide referral criteria, all CKD stages and all renal diseases were represented [27].

The frequency of nephrological and obstetric visits was individualized (range in the outpatients on the diet: weekly to twice monthly). Patients hospitalized in the obstetrics ward were controlled by the nephrologist at least once weekly. Hospitalization was required in the presence of poorly controlled hypertension or new onset hypertension, worsening of renal function, new onset or worsening of proteinuria, upper urinary tract infection and any intercurrent problem (including abnormal fetal growth and severely abnormal umbilical Doppler).

At each consultation, blood pressure was measured and weight was recorded; fetal well-being was assessed by ultrasound and growth was controlled by serial measurements of symphysis–fundal height. Controls of ultrasound biometry and Doppler velocimetry of uterine and umbilical arteries were individualized (biometry every 2–3 weeks in the case of fetal growth restriction with Doppler assessment two to four times weekly in the case of Doppler anomalies).

All patients were instructed to measure blood pressure at home and immediately report any problems referred early to the unit. Twenty-four-hour blood pressure measurement was employed in the case of discrepancies between consultations and diary, or to assess nocturnal dipping.

Besides the routine controls of pregnancy (viral data, toxoplasma serology, etc.), all patients underwent, at least, a monthly determination of renal function and proteinuria, uric acid, urinalysis and urinary culture, serum electrolytes, coagulation parameters and blood cell counts. Other laboratory data were required on demand.

The therapeutic blood pressure goal was ≤130/80 mmHg. Drugs of choice were nifedipine or α-methyldopa, the latter preferred in case of intense proteinuria or peripheral edema. Beta blockers or doxazosine were employed in the case of insufficient response or severe side effects with the above drugs.

In every case, the aim was to delay delivery as much as possible until 34–36 weeks. Indications for early delivery were severe worsening of maternal and/or fetal conditions up to 32 weeks of gestational age, or less severe worsening after 32 weeks. Caesarean section was performed for fetal indications, before or during labour, or in cases of unfavourable conditions for induction (including prematurity) or lack of response to induction.

Indication for the diet and dietary regimen

The main indications for the low-protein vegetarian diets were pregnancy in patients already on a supplemented vegetarian diet, severe CKD, severe proteinuria or a combination of the abovementioned data, particularly in patients early referred to the Unit, as we felt that the effect of the diet was minor in cases of late referral. The diet was thus proposed only to patients meeting the following criteria: early referral (before the 20th week of gestation), severe proteinuria at referral, CKD stage 3–5 or both. Severe proteinuria was initially defined as nephrotic proteinuria at referral (2000–2006). However, over time the definition widened, presently including proteinuria >1 g/day at referral. Exclusion criteria were the presence of a socio-cultural or a language barrier that would have severely affected the possibility of a correct management of the diet, psychiatric problems affecting compliance and clinical history of anorexia or bulimia. These criteria are somehow questionable, as they reflect the caregivers' opinions, but we felt that, at least until better understanding of the diet was attained, adding the diet to a complex regimen of controls could negatively affect compliance to 'life saving' therapies in women with baseline compliance problems. In one case, only the diet was not proposed because of the presence of a dietary regimen with 'aproteic' foods, prescribed in a different setting and followed with optimal compliance (IgA nephropathy, CKD stage 3, proteinuria 0.5 g/day at start of pregnancy).

Thus, >168 pregnancies were referred in the context of a referral policy of early CKD stages in pregnancy; a further 15 cases would have met the present clinical selection criteria (early referred stages 3–4 CKD; severe proteinuria). Two patients spontaneously terminated pregnancy (early abortions) while being evaluated. Besides the patient already on a different protein-restricted diet, the reasons for not proposing the diet were psychiatric problems or previous anorexia in three cases, language and logistic barriers in six pregnancies in four patients (in one of them three pregnancies were observed, two of which terminated, one for maternal and one for fetal reasons). The three remaining cases were observed in the first period of study and were not included on account of subnephrotic proteinuria. One further patient, not included in the present series, which

takes into account only patients who delivered, is presently on the diet (28th week of gestation).

Within these selection criteria, all the patients who were offered this option initially tried and subsequently followed the vegetarian supplemented diet throughout pregnancy.

The low-protein diet consisted in an adaptation of the usual low-protein vegetarian diet employed in our centre (protein: 0.6 g/kg/day, on ideal weight, supplemented with the commercial keto-analogues: ketosteril one pill/10 kg body weight, one to two free meals/week).

In an empirical attempt to balance the advantages of low-protein diets in CKD and the habit of increasing protein intake in pregnancy, we adjusted the diet to 0.6–0.7 g/kg/day of protein, based on pre-conception weight, increasing the supplementation with keto-analogues to one pill/8 kg body weight in the first and second trimester, and one pill/5 kg body weight in the third trimester. According to the functional status, and to patients' needs and preferences, one to three free meals were allowed per week. Iron, B_{12} or calcium supplements were employed on the basis of the biochemical results. Erythropoietin was used when needed, with a haemoglobin target of 10–11 g/dL, on account of the haemodilution of pregnancy.

In the absence of reports on the specific mixture of keto-acids and amino acids in pregnancy, efforts were made to control for risks linked to the protein content and to the additives. At the time of the study, no report on those issues had been found or made available by the company.

Informed consent was obtained: patients were instructed that no previous data on the supplemented diet during pregnancy were available, and they were extensively counselled on the limits and goals of the diet, and on the importance of the timely reporting of any side effect.

Compliance was evaluated by the nephrologist and by the dieticians by means of dietary recall, since the commonly employed Mitch formula, based on urinary urea, is not validated in pregnancy due to the anabolic nature of this condition. Compliance to keto-acids was indirectly recorded: the patients received the dietary supplements on occasion of the clinical controls and at such times they were asked about their needs, and the number of pills consumed was thus indirectly calculated.

Before pregnancy, caloric intake was calculated as 30–35 kcal/kg 'ideal' body weight, according to the type of physical activity (working or sport). In pregnancy, the patients were evaluated by the dietician of the Materno-Foetal Unit, and efforts were made to maintain an adequate caloric intake. The formulae used by the dieticians of the unit are based on the calculation of the basal metabolism, plus 100–300 kcal/day, since the 12–14th week of pregnancy, according to physical activity (reduced in the case of prolonged bed rest) [28]. However, as the diet is very demanding, efforts were made not to further ask the patients to weigh the food at every meal, and the indications on the quantities were defined as baseline and adjusted in periodic controls according to the weight gain/loss, the presence of edema and the patient's recall.

Results

Baseline data

The main baseline data on the 12 pregnancies are reported in Table 1. The patients treated with the diet account for about 7% of all pregnancies recorded in the CKD population followed in our multidisciplinary outpatient unit (12/168 referred in February 2010).

In two cases on a supplemented diet before pregnancy, the baseline diet was continued, increasing the supplement dose, throughout pregnancy (second pregnancy in Patient 2 and Patient 6; Table 1). In the other cases, the diet was prescribed as a 'rescue treatment' in very high-risk pregnancies: of note, two patients (Cases 7 and 10) had been counselled to terminate their pregnancies in other settings. The main indication for the diet was severe CKD (stages 3–4 in five patients) and/or severe proteinuria. Proteinuria was considered as severe when it was at least 1 g/day at the start of pregnancy. This was present in nine cases in this series, and in four a full-blown nephrotic syndrome was present. In five patients, both severe proteinuria and severe CKD co-existed (Table 1). Of note, pregnancy had been strongly discouraged in different settings in several patients (Cases 1, 4 and 10), and Patient 7 terminated a previous pregnancy following the advice of her previous caregivers who considered her situation non-compatible with materno-fetal favourable outcomes.

Pre-conception data were available in nine cases. While a trend towards an increase in GFR and a decrease in serum creatinine was observed in most cases, only two patients (Cases 7 and 9) were reclassified at the first control in pregnancy (from stage 3 to stage 2). The low BMI and body weight in our population, according to the northern Italian standards, account for the relatively low creatinine levels [27].

Pregnancy outcomes and follow-up: the mother

In the setting of a strict control policy, no side effects of the diet or of the supplements were reported. Abdominal discomfort, due to pregnancy-associated nausea, was frequent during the first 12–14 weeks, but the patients who had started the diet early referred no change during the free meals.

According to dietary recall, all patients followed the diet with good to very good compliance. One patient, the second pregnancy of Patient 2, was left free to alternate the supplemented diet with a free diet, on the account of anorexia and frequent vomiting, in the setting of stable kidney function.

One patient chose to terminate her pregnancy on account of clinical (nephrotic syndrome) and logistical problems (need for long hospitalization, far from home, language barrier). She underwent a renal biopsy after pregnancy termination, with a diagnosis of membranous nephropathy.

The diet was continued up to delivery in the other 11 pregnancies.

Two patients were affected by systemic lupus erythematosus (Cases 4 and 10). In both cases, the diet was undertaken in the attempt to control proteinuria, already elevated at baseline. The first patient experienced a cutaneous and articular flare-up around the 30th week of pregnancy, leading to increased steroid therapy and to anticipate delivery at the 32nd week. Patient 10 started pregnancy in a nephrotic flare, which was linked to self-discontinuation of steroid therapy. At referral in our centre, she was treated with bolus steroids, and azathioprine was started, slowly tapering steroids (25–7.5 mg from referral to delivery). Proteinuria decreased in the first trimester and stabilized thereafter. No clinical or biochemical flare-up was observed.

Three patients were affected by diabetic nephropathy (Patient 1; two pregnancies in Patient 2; Patient 7). In all cases, the metabolic control during pregnancy was very good, with glycated haemoglobin stable (<7%) in all. However, it is difficult to disentangle the effect of the diet from the effect of a very strict glycaemic control, as all patients were shifted to microinfusion pumps and clinical controls were intensified.

Table 1. Main baseline data

Case	Age at start	Referral to the unit—pre-conceptional evaluation	Renal disease	sCr mg/dL (GFR mL/min)	CKD stage (K-DOQI)	Ptu (g/24 h)	BUN (mg/dL)	Protein/albumin (g/dL)	Hypertension (Y/N) and therapy	Therapies at referral or during first hospitalization	BMI (weight) pre-con
1	35	Follow-up and pre-conceptional evaluation; intracytoplasmic sperm injection (ICSI) followed in the Unit	Diabetic nephropathy (type 1 diabetes)	1.2 (52)	3	2.5	21	5.9/2.8	Yes (normal at start)	Insulin, folate	23.5 (72)
2 (2 preg.)[a]	35	Follow-up and pre-conceptional	Diabetic nephropathy (type 1 diabetes)	1.2 (55)	3	5.9	16	5.8/3.2	No[b]	Insulin, B_{12}, ferrum, vitamins	22 (50)
	37	evaluation; referral: 8th and 6th weeks		1.6 (48)	3	1.8	22	6.5/3.8	No[b]	Insulin, folate	22 (50)
3	28	Regular follow-up; referral: 7th week	Medullary sponge kidney	3.2 (20)	4	0.8	54	6.5/3.53	No	erithropoietin (EPO), vitamin D, folate	22 (56)
4	32	Irregular follow-up; referral: 6th week	Lupus nephropathy	0.7 (124)	1	2.7	20	6.0/3.1	Yes	Prednisone, folate, ASA, omeprazole, α-methyldopa	24 (65)
5	26	Diagnosis of nephrotic syndrome in pregnancy; referral: 18th week	Biopsy post-termination: membranous GN	0.6 (135)	1	5.5	5	5.1/2.3	No	Bolus steroids at hospitalization, heparin	19 (57)
6[a]	35	Follow-up and pre-conceptional, evaluation; referral: 7th week	Interstitial nephropathy (reflux)	3.2 (27)	4	1.0	50	8.4/4.5	Yes	Vitamin D, low dose beta blocker, folate, ferrum, ASA	19 (46)
7	29	Irregular follow-up; referral: 9th week	Diabetic nephropathy (type 1 diabetes)	1.5 (66)	2	6.3	29	6.6/3.6	Yes	Insulin, nifedipine, folate	20 (63)
8	38	Diagnosis of nephrotic syndrome in pregnancy; referral: 17th week	Biopsy after pregnancy: membranous GN	0.6 (121)	1	3.6	9	5.8/2.6	No	None	22 (54)
9	32	Regular follow-up; referral: 6th week	Renal graft	1.2 (66)	2	0.5	35	6.9/4	Yes (normal at start)	CyA, prednisone, folate B_{12}, ranitidine, ASA	24 (62)
10	20	Irregular follow-up; referral: 5th week	SLE, MPGN	0.6 (125)	1	2.5	17	6.8/3.3	No	Bolus steroids, ASA, omerazole, folate	21 (53)
11	37	Follow-up and pre-conceptional evaluation; referral: 7th week	Renal graft	1.5 (47)	3	0.8	39	7.0/3.9	Yes	CyA, prednisone, vitamin D, nifedipine, folate, ASA, EPO, ferrum, ranitidine	27 (74)

Age: age at start of pregnancy. Data at referral: first control when the patient started follow-up in our Unit. When two pieces of data were available in the week of referral, an average was calculated.
BMI: body mass index; pre-con: BMI before pregnancy; SLE: systemic lupus erythematosus; ASA: acetylsalicylate; MPGN: membranous and proliferative GN; GN: glomerulonephritis; CyA: cyclosporine A; Ptu: proteinuria on 24-h urine collection; sCr: serum creatinine; GFR: glomerular filtration rate.
[a]Patients already on a supplemented low-protein diet.
[b]ACE inhibitors for proteinuria, discontinued at positive pregnancy test.

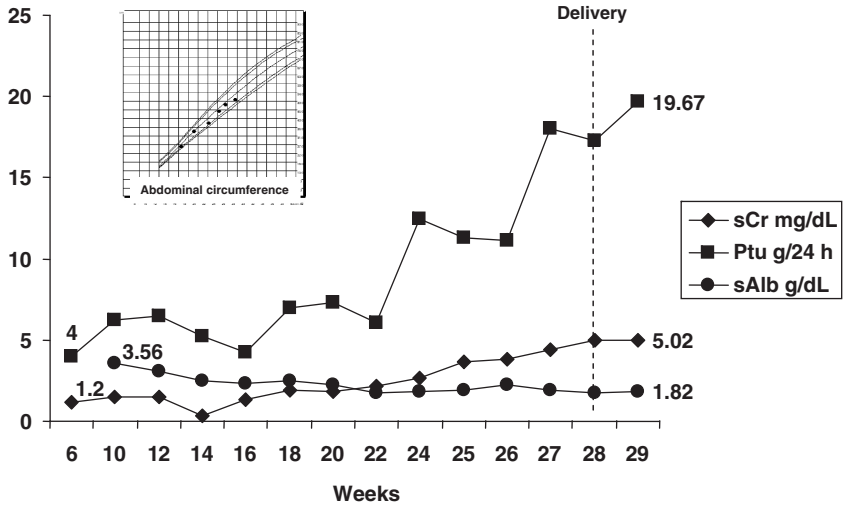

Fig. 1. Case 7. Preterm delivery in the context of severe proteinuria and worsening of the kidney function. Regular foetal growth.

Only one case (Case 7) doubled serum creatinine during pregnancy; her data are reported in Figure 1. In spite of the presence of a sharp increase in proteinuria and a progressive decrease in GFR, with slow increase in serum creatinine, the growth curve of her baby was regular (abdominal curve is shown in the figure). The decision to perform the caesarean section at the 28th week of gestation was on account of the worsening of maternal data.

Overall, a stage shift was observed in three cases: Cases 7 and 2 (Figures 1 and 2), and in Case 9, considering the data at the end of pregnancy. Considering the data 3 months after delivery, two cases improved their renal function as compared with delivery (Cases 7 and 9), while one case shifted to a subsequent CKD stage (Case 3, Figure 3). Excluding the patient who was later diagnosed with membranous nephropathy (Case 8), the trend at 3 months was towards a decrease in proteinuria, at baseline levels (Table 2).

Overall, serum albumin increased at 3 months after delivery in spite of the fact that four cases, two with severe CKD and two with nephrotic syndrome, breast-fed their babies for at least 3 months. The rise in serum albumin was observed in the women who continued the diet as well as in those who discontinued it.

The diet was discontinued after delivery in six cases (Cases 4, 5, 8, 9, 10 and 11). In four of them, the primary goal had been the control of proteinuria. In two cases, both kidney transplant recipients, the usual dietary regimen with ~1 g/kg/day of protein was resumed after delivery.

Pregnancy outcomes and follow-up: the babies

The main data at delivery and the outcome of the offspring are reported in Table 3.

Only two babies, whose mothers had the most severe kidney function impairment (Cases 4 and 6), were classified as SGA at birth (Table 3). The first case (Case 3) had developed IUGR (Figure 3) with the flattening of the

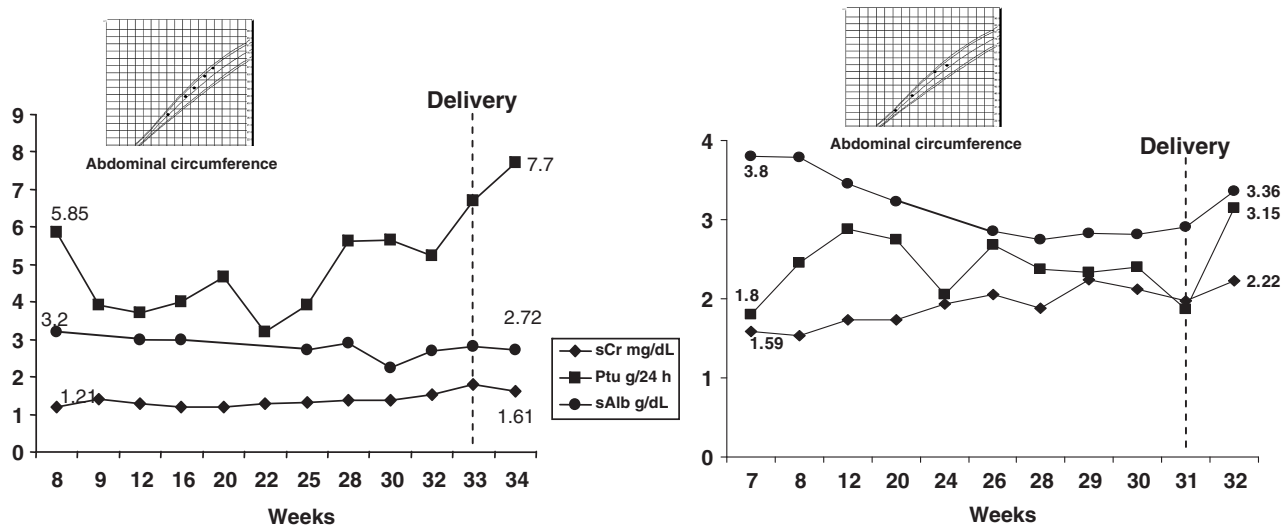

Fig. 2. The two pregnancies of Case 2. Regular foetal growth in spite of the baseline GFR and proteinuria.

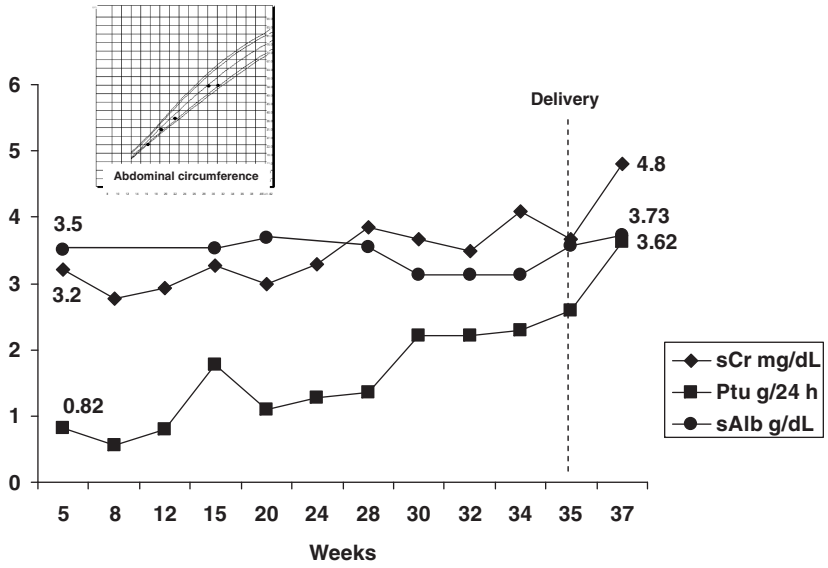

Fig. 3. Case 3: IUGR (intrauterine growth restriction): flattening of the growth curve.

growth curve along with abnormal umbilical Doppler. The second case (Case 6) had a growth curve at the 10th centile with occasional pathologic umbilical Doppler. The mother was of very small frame (pre-conception BMI: 19, weight 46 kg, height 157 cm), suggesting a constitutionally small but otherwise normal baby (Figure 4). Interestingly, a previous pregnancy, followed in another nephrology setting, and managed with a free diet, resulted in caesarean section at the 30th week of a female baby also classified as SGA (5–10th centile).

In 9/11 babies, the delivery was by caesarean section, 10/11 were delivered pre-term (median week of delivery: 32 weeks; range 28–37 weeks) and 8/11 needed at least a few days of support in the neonatal intensive care unit (NICU) (Tables 2 and 3).

At the time of the present analysis (March 2010), all the babies are well, with normal development, at 1 month–7.5 years from delivery.

Discussion

The present study stems from the combination of two hot topics in nephrology: the limits and advantages of low-protein diets [11–18] and the challenges of pregnancy in CKD patients [1–9]. The latter problem will probably increase because of the combination of higher prevalence and diagnosis of CKD, increasing childbearing age, and a more open attitude towards high-risk pregnancies [1–9,28,30]. In spite of the vast literature on these emerging aspects of renal care, there is an almost complete lack of studies on low-protein diets in pregnant CKD women.

The potential of the diet in pregnancy is of great interest both to avoid the long-term tapering off of residual renal function and as a 'rescue treatment' in the management of very complex patients who desperately want to have a baby. Thus, in the present study, we analyse a first cohort of pregnant CKD patients managed with an adapted regimen of supplemented low-protein diet. The subset of patients represents a negative selection from the population referred to our tertiary Materno-Foetal Unit (~7% of pregnancies in CKD: six patients were in CKD stage 3–4 and four had a nephrotic syndrome) [27]. For some of the patients, the pregnancy under study was the 'last chance' before dialysis or transplantation. Pregnancy had been strongly discouraged in many patients, and one had interrupted a previous pregnancy, considered as non-compatible with favourable outcome, in a different setting (Table 1).

The analysis of the renal function and of nutritional data in pregnancy is an unmet challenge [6–10,30]. In fact, serum albumin, total protein and haemoglobin physiologically decrease in pregnancy [6]. Even in the absence of overt oedema, 'dry' weight gain is difficult to assess, as pregnancy is a situation of expanded volumes [6–10]. Urinary urea is not a reliable marker of protein intake in an anabolic condition such as pregnancy. Proteinuria tends to increase throughout pregnancy, particularly in patients who are already proteinuric, while serum creatinine should maintain a decreasing trend, at least in the first trimester, due to absolute or relative hyperfiltration [6–10].

Therefore, our feasibility study was limited to clinical observations and was focused on three issues: the presence/absence of side effects of the diet or of the supplements, the outcome of the mother and child, and the fetal growth pattern. Since it is impossible to disentangle the effects of the diet from those of other therapeutic tools, complex multiple therapies and strict follow-up, including long hospitalization periods with frequent monitoring and bed rest, the context sensitivity of our study should also be underlined.

None of the patients reported any side effect of the diet or of the supplements, including abdominal discomfort. The monotony of the dietary regimen was the main (albeit usually minor) complaint, particularly during the long hospitalization periods (Table 2). One patient reported anorexia during her second pregnancy (both on

Table 2. Main data at delivery[a]

Case	Week of delivery	sCr mg/dL (GFR mL/min)	CKD stage	Ptu (g/24 h)	BUN (mg/dL)	Total protein/ albumin	Weight gain (kg) (%)	Hospitalization in pregnancy (post-partum)	Long-term outcome of the mother	sCr (GFR) at 3 months	Proteinuria (g/day)/ s-albumin (g/dL) at 3 months
1	31	1.8 (53)	3	6.2	25	4.8/1.9	9 (13.4%)	95 (8)	Pancreas kidney graft, 2 years after delivery	2.0 (45)	3/2.5
2	33	1.8 (45)	3	5.6	20	5.7/2.8	11 (20%)	73 (11)	On follow-up (diet)	1.9 (40)	4/3
(2 pregn.)	31	2.0 (21)	4	1.9	22	5.6/2.9	9 (18%)	47 (8)		2.1 (21)	1.5/3.1
3[a]	35	3.7 (18)	4	2.6	53	6.3/3.6	9 (16%)	55 (6)	Pre-emptive kidney graft, 1 year after delivery	4.5 (10)	0.8/3.6
4[a]	32	0.7 (125)	1	3.4	10	4.8/2.1	14 (21.5%)	123 (9)	On irregular follow-up	na	na
6[a]	31	2.9 (20)	4	2.0	44	6.2/2.9	10 (21.7%)	80 (5)	On follow-up (diet)	2.8 (25)	1.5/3.5
7	28	5.0 (10)	5	17.3	29	4.2/1.8	16 (25%)	93 (9)	On follow-up (diet)	4.3 (19)	5/3.1
8[a]	37	0.6 (148)	1	2.1	7	5.0/2.4	10 (20%)	30 (3)	Kidney biopsy: membranous GN	0.8 (120)	4/3.2
9	34	1.3 (55)	3	3.6	23	5.3/2.8	8 (12%)	84 (6)	On follow-up for the kidney graft	1.2 (64)	1.3/na
10	34	0.5 (120)	1	2.9	30	5.4/2.7	11 (17%)	63 (8)	On follow-up (SLE remission)	[b]	–
11	33	1.8 (40)	3	5.4	26	5.4/2.8	5 (7%)	99 (9)	On follow-up for the kidney graft	[b]	–

The patient who terminated pregnancy (Case 5) is not reported.
[a]Patients who breast-fed their babies for at least 2 months.
[b]Patients with <3 months follow-up.

Table 3. Outcome of the babies in February 2010

Case	Gestational age at delivery (weeks)	Type of delivery	Main reasons for delivery	Sex	Weight (g)	Centile	Apgar score (1 min, 5 min)	Need for NICU	Hospitalization (days)	Follow-up of the baby
1	31	Vaginal	Spontaneous labour	M	1590	10–50	7–8	Yes	24	7.5 years
2 (2 preg.)	33	Caesarean	No response to induction (increasing BP)	F	1980	10–50	9–9	Yes	15	4.5 years
	31	Caesarean	Spontaneous labour; caesarean for retinopathy	M	1970	50–90	8–8	Yes	21	19 months
3	35	Caesarean	No response to induction (IUGR)	F	1685	<5	8–9	Yes	15	28 months
4	32	Caesarean	SLE flare-up	M	2080	50–90	9–9	No	8	24 months
6	34	Caesarean	Increase in proteinuria and pathologic Doppler	F	1410	<5	8–8	Yes	23	9 months
7	28	Caesarean	Worsening of maternal conditions	F	935	10–50	7–8	Yes	77	9 months
8	37	Vaginal	Induction at term	M	2620	50–90	9–9	No	7	5 months
9	34	Caesarean	Increase in blood pressure; 'security term' reached. Caesarean: mother's choice	M	2180	10–50	8–9	No	6	5 months
10	34	Caesarean	Spontaneous rupture of membranes, pathologic trace in labour	F	1710	10–50	9–9	Yes	15	1 month
11	33	Caesarean	Hypertensive crisis and increase in proteinuria in previous caesarean	F	2115	50–90	7–8	Yes	7	1 month

The patient who terminated pregnancy (Case 5) is not reported.

the vegetarian diet); for this reason, she was left free to alternate vegetarian and free diets. She did not report any specific difference in her eating pattern with the two regimens. No patient developed hyperkalaemia or hypercalcaemia. Indeed, the increased calcium need in pregnancy may have a protective role on this supplement side effect in pregnancy.

Compliance was very good in all patients, as assessed by periodic dietary recall and shown by the low blood urea nitrogen (BUN) levels, considered as a surrogate indicator of dietary protein intake in pregnancy, in the absence of reliable formulae (Table 2). However, the control schedule was very tight, with an average of three controls per month and very long periods of hospitalization in all patients (Table 2). It should also be mentioned that this very demanding diet was not proposed if a compliance problem was anticipated, and the present cohort is the result of the balance between a clinical (negative) and attitudinal (positive) balance. The promising results obtained will probably lead to further widening of our enrolment criteria in the future.

Regarding the renal function data, only one patient doubled serum creatinine and sharply increased proteinuria (Figure 1, Case 7). Interestingly, her renal function improved after delivery, an unusual pattern in contrast to the usual increase in serum creatinine after interruption of the hyperfiltration stimulus represented by pregnancy [6–10] (Table 2). Two further patients shifted by one CKD stage (Cases 2 and 9). Patients 2 and 7 were diabetic and Patient 9 was a renal graft recipient, thus underlying the importance of a further hyperfiltration challenge in these patients.

No patient started dialysis during pregnancy or within the first year thereafter, nor developed complications of the nephrotic syndrome or of delivery; indeed, in spite of long hospitalizations during pregnancy, all patients were discharged according to our usual policy (Table 2).

The data are in line with those observed with our overall population of CKD patients [27] and with the literature data [1–6]. While our data do not allow the demonstration of a favourable effect of the diet, at least they suggest that a negative effect on the mother is unlikely. In this regard, our data may confirm the previous observation of no differences in the outcomes of babies born from vegetarian versus non-vegetarian mothers [31].

The low albumin levels at delivery are presumably both an effect of physiological haemodilution and of renal losses. After pregnancy, the trend was towards an increase in serum albumin and decrease in proteinuria, with the exception of Patient 8, whose proteinuria displayed wide variations, in keeping with her bioptic diagnosis of membranous nephropathy. Interestingly, albumin levels increased similarly in the cases that discontinued or continued the diet, thus suggesting that the low levels are pregnancy related and not diet related (Table 2).

Babies born from CKD mothers are often reported to be SGA and/or affected by IUGR [1–9,27,36]. In this relatively small series, 9/11 babies displayed a normal growth (Figures 1–4; Table 3). Taking into account the literature data, showing an overall incidence of SGA and IUGR in the range of 20–40% of the babies born, our data support

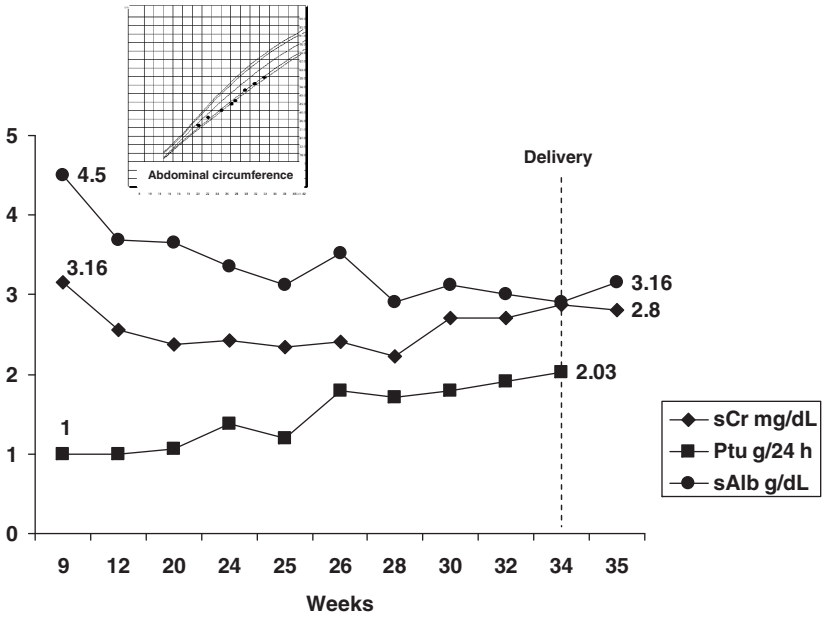

Fig. 4. Case 6. SGA: small for gestational age baby, regularly growing on her own growth curve.

the fact that the diet did not have a detrimental effect on fetal growth. In keeping with this observation, within the limits of a relatively short follow-up, all the babies are well, developing normally, 1 month–7.5 years from delivery. All the patterns of intrauterine growth were observed, including normal growth pattern (Case 2), with relatively stable kidney function or observed in spite of worsening of maternal conditions (Case 7), SGA (Case 4) and with IUGR at the last control (Case 3). They are reported in Figures 1–4.

There is no evidence supporting the use of high-protein diets in pregnancy, and a few studies even suggest that they may be harmful [32]. It must be acknowledged, however, that very low-protein regimens may have a negative effect on kidney development and represent a risk for future diseases [32–35]. Nevertheless, our knowledge on the risks of malnutrition stems from studies in the developing world or from animal models (usually employing a protein content 50–70% lower than usual). In both cases, protein reduction is extreme and not comparable with the moderate reduction prescribed in our regimen [32–35].

However, it has to be underlined that, in spite of these positive data in a negatively selected population, and in keeping with the experience of our group and of others' in high-risk CKD patients, caesarean section was needed in most of the cases (9/11 deliveries), and 10/11 babies were pre-term (6/10 <34 weeks), thus underlining once more the challenges of pregnancies in severe CKD and severe proteinuria [1–9,27]. Even if the role of proteinuria in CKD patients' pregnancy is not yet clear, it may not only represent an important risk factor for the progression of CKD but also a confounding element due to the difficult differential diagnosis with pre-eclampsia in baseline proteinuric disorders. Further, proteinuria may be a complicating factor, considering the hypercoagulative state of pregnancy. In this context, since ACE inhibitors and angiotensin receptor blockers are banned in pregnancy, low-protein diets remain the main therapeutic option for controlling proteinuria [36,37].

Our study has some strengths and several weaknesses.

It has the main strength of being the first report on a series of high-risk pregnancies in CKD patients managed by supplemented low-protein vegetarian diets throughout pregnancy, and of reporting on a series of babies followed by the same group, with regular assessment of the growth curves.

Its several limitations are partly intrinsic (limits to the analysis of renal function and proteinuria in CKD pregnancies; lack of validated data on the nutritional assessment in pregnancy) and partly shared by observational studies on new approaches in the clinically and ethically complex field of high-risk pregnancies [1–9,27].

A control group in our series is lacking, as the diet was considered a rescue approach in complex cases, and was systematically offered to all patients with severe CKD, proteinuria and early referral, in which this approach was feasible and integrated with the daily habits. Randomization was not felt to be feasible or ethical in such a context. Moreover, it was not possible to separate the effects of the diet from those of the other therapies, including long-term hospitalization, very strict monitoring or bed rest. Furthermore, the baseline conditions of the patients were highly heterogeneous. Nevertheless, these biases are shared by most single-centre studies on high-risk pregnancies and can be partly overcome only by large multi-centre analyses.

Our feasibility study suggests the need for further observational studies in different clinical contexts and for interventional studies in selected populations. Long-term follow-up of the offspring is needed both in children exposed to the maternal diet and in children born to CKD mothers on different dietary regimens.

Conclusion

Pregnancy is a great challenge for CKD patients and yet a major determinant of the quality of life [1–9,27,34,35]. In the absence of literature data, our report suggests that a supplemented vegetarian diet is a safe option in pregnant CKD patients and that it can be considered a tool to be cautiously employed in the tailored clinical management of these complex high-risk conditions.

Conflict of interest statement. The authors declare that the results presented in this paper have not been previously published, in whole or in part, except in abstract format.

References

1. Williams D, Davison J. Chronic kidney disease in pregnancy. *BMJ* 2008; 336: 211–215
2. Hou S. Historical perspective of pregnancy in chronic kidney disease. *Adv Chron Kidney Dis* 2007; 14: 116–118
3. Fischer MJ, Lehnerz SD, Hebert JR *et al*. Kidney disease is an independent risk factor for adverse fetal and maternal outcomes in pregnancy. *Am J Kidney Dis* 2004; 43: 415–423
4. Tandon A, Ibañez D, Gladman DD *et al*. The effect of pregnancy on lupus nephritis. *Arthritis Rheum* 2004; 50: 3941–3946
5. Cavallasca JA, Laborde HA, Ruda-Vega H *et al*. Maternal and fetal outcomes of 72 pregnancies in Argentine patients with systemic lupus erythematosus (SLE). *Clin Rheumatol* 2008; 27: 41–46
6. Maynard SE, Thadhani R. Pregnancy and the kidney. *J Am Soc Nephrol* 2009; 20: 14–22
7. Imbasciati E, Gregorini G, Cabiddu G *et al*. Pregnancy in CKD stages 3 to 5: fetal and maternal outcomes. *Am J Kidney Dis* 2007; 49: 753–762
8. Bar J, Ben-Rafael Z, Padoa A *et al*. Prediction of pregnancy outcome in subgroups of women with renal disease. *Clin Nephrol* 2000; 53: 437–444
9. Chopra S, Suri V, Aggarwal N *et al*. Pregnancy in chronic renal insufficiency: single centre experience from North India. *Arch Gynecol Obstet* 2009; 279: 691–695
10. Conrad KP. Mechanisms of renal vasodilation and hyperfiltration during pregnancy. *J Soc Gynecol Investig* 2004; 11: 438–448
11. Bergstrom J. Discovery and rediscovery of low protein diet. *Clin Nephrol* 1984; 21: 29–35
12. El Nahas AM, Coles GA. Dietary treatment of chronic renal failure: ten unanswered questions. *Lancet* 1986; 1: 597–600
13. Mitch WE. Dietary therapy in CKD patients—the current status. *Am J Nephrol* 2005; 25: S7–S8
14. Walser M, Mitch WE, Maroni BJ *et al*. Should protein intake be restricted in predialysis patients? *Kidney Int* 1999; 55: 771–777
15. Fouque D, Wang PH, Laville M *et al*. Low protein diets for chronic renal failure in non diabetic adults. *The Cochrane Library* 2005; 4
16. Giovannetti S. Supplemented diet for severe chronic renal failure: some controversial points. *Contrib Nephrol* 1989; 75: 147–154
17. Jungers P, Chauveau P. Amino acids and keto acids in the treatment of chronic renal failure. *Blood Purif* 1988; 6: 299–314
18. Teplan V. Pharmacological features of a keto amino acid therapy. *Am J Nephrol* 2005; 25: S13–S14
19. National Collaborating Centre for Women's and Children's Health. Antenatal care: routine care for the healthy pregnant woman. Clinical Guideline. London: RCOG Press, 2008
20. Millward DJ. Optimal intakes of protein in the human diet. *Proc Nutr Soc* 1999; 58: 403–413
21. Aggett PJ, Bresson J, Haschke F. Recommended Dietary Allowances (RDAs), Recommended Dietary Intakes (RDIs), Recommended Nutrient Intakes (RNIs), and Population Reference Intakes (PRIs) are not "recommended intakes". *J Pediatr Gastroenterol Nutr* 1997; 25: 236–241
22. Symonds ME, Stephenson T, Gardner DS *et al*. Long-term effects of nutritional programming of the embryo and fetus: mechanisms and critical windows. *Reprod Fertil Dev* 2007; 19: 53–63
23. Yakoob M, Menezes EV, Soomro T *et al*. Reducing stillbirths: behavioural and nutritional interventions before and during pregnancy. *BMC Pregnancy and Childbirth* 2009; 9: S3
24. National Kidney Foundation. KDOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. *Am J Kidney Dis* 2002; 39: S1–S266
25. Parazzini F, Cortinovis I, Bortolus R *et al*. Standards of birth weight in Italy. *Ann Ostet Ginecol Med Perinat* 1991; 112: 203–246
26. Adamkin DH. Late preterm infants: severe hyperbilirubinemia and postnatal glucose homeostasis. *J Perinatol* 2009; 29: S12–S17
27. Piccoli GB, Attini R, Vasario E *et al*. Pregnancy and chronic kidney disease: a challenge in all CKD stages. *Clin J Am Soc Nephrol* 2010; 5: 844–855
28. Lof M, Olausson H, Bonstrom K *et al*. Changes in basal metabolic rate during pregnancy in relation to changes in body weight and composition, cardiac output, insulin-like growth factor I, and thyroid hormones and in relation to fetal growth. *Am J Clin Nutr* 2005; 81: 678–685
29. Piccoli GB, Mezza E, Grassi G *et al*. A 35 year old woman with diabetic nephropathy who wants a baby: case presentation. Interactive case report. *BMJ* 2004; 329: 674
30. Piccoli GB, Conijn A, Consiglio V*et al*. Pregnancy in dialysis patients: is the evidence strong enough to lead us to change our counseling policy? *Clin J Am Soc Nephrol* 2010; 5: 62–71
31. Position of the American Dietetic Association: vegetarian diets. *J Am Diet Assoc* 2009; 109: 1266–1282
32. Merialdi M, Carroli G, Villar J *et al*. Nutritional interventions during pregnancy for the prevention or treatment of impaired fetal growth: an overview of randomized controlled trials. *J Nutr* 2003; 133: S1626–S1631
33. Langley-Evans SC, Langley-Evans AJ, Marchand MC. Nutritional programming of blood pressure and renal morphology. *Arch Physiol Biochem* 2003; 111: 8–16
34. Wintour EM, Johnson K, Koukoulas I *et al*. Programming the cardiovascular system, kidney and the brain—a review. *Placenta* 2003; 24: S65–S71
35. Harrison M, Langley-Evans SC. Intergenerational programming of impaired nephrogenesis and hypertension in rats following maternal protein restriction during pregnancy. *Br J Nutr* 2009; 101: 1020–1030
36. Ganesvoort RT, de Zeeuw D, de Jong PE. Additive antiproteinuric effect of ACE inhibition and a low protein diet in human renal disease. *Nephrol Dial Transplant* 1995; 10: 497–504
37. Fouque D, Aparicio D. Eleven reasons to control the protein intake of patients with chronic kidney disease. *Nat Clin Pract* 2007; 3: 383–392

Received for publication: 24.3.10; Accepted in revised form: 25.5.10