

## Severe Diabetic Nephropathy in Type 1 Diabetes and Pregnancy – A Case Series

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Manuscript submitted March 7, 2013; resubmitted April 16, 2013; accepted April 25, 2013

### ■ Abstract

**BACKGROUND:** Diabetes and nephropathy are important challenges during pregnancy, increasingly encountered because of the advances in maternal-fetal care. **AIM:** To evaluate the maternal and fetal outcomes recorded in “severe” diabetic nephropathy in type 1 diabetic patients referred to nephrological healthcare. **METHODS:** The study was performed in an outpatient unit dedicated to kidney diseases in pregnancy (with joint nephrological and obstetric follow-up and strict cooperation with the diabetes unit). 383 pregnancies were referred to the outpatient unit in 2000-2012, 14 of which were complicated by type 1 diabetes. The report includes 12 deliveries, including 2 pregnancies in 1 patient; one twin pregnancy; 2 spontaneous abortions were not included. All cases had long-standing type 1 diabetes (median of 21 (15-31) years), relatively high median age (35 (29-40) years) and end-organ damage (all patients presented laser-treated retinopathy and half of them clinical neuropathy).

Median glomerular filtration rate (GFR) at referral was 67 ml/min (48-122.6), proteinuria was 1.6 g/day (0.1-6.3 g/day). **RESULTS:** Proteinuria steeply increased in 11/12 patients, reaching the nephrotic range in nine (6 above 5 g/day). One patient increased by 2 chronic kidney disease (CKD) stages. Support therapy included blood pressure and diabetes control, bed rest, and moderate protein restriction. All children were preterm (7 early preterm); early spontaneous labor occurred in 4/12 patients. All singletons were appropriate for gestational age and developed normally after birth. The male twin child died 6 days after birth (after surgery for great vessel transposition). **CONCLUSIONS:** Diabetic patients with severe diabetic nephropathy are still present a considerable challenge. Therefore, further investigations are required, particularly on proteinuria management and the occurrence of spontaneous labor.

**Keywords:** type 1 diabetes · diabetic nephropathy · pregnancy · pre-term delivery · nephritic syndrome

### Introduction

**D**iabetes and nephropathy are highly significant challenges during pregnancy [1-8]. In the last few decades, the so-called “high-risk pregnancies” have become more frequent and increasingly recognized, mainly as a reflection of the advances in maternal-fetal care and of the updated

definitions of several diseases, including chronic kidney disease (CKD). In particular, CKD prevalence during pregnancy has markedly increased because of the new definitions of CKD in the Kidney Disease Outcomes Quality Initiative (K-DOQI) guidelines since 2000 [9-10]. In spite of the growing interest, our knowledge is still relatively limited. This is also the case for diabetes and severe

kidney disease during pregnancy, pathological scenarios where the definitions are crucial for risk assessment [11].

A review of the literature of the last decade underlines not only the persistence of a higher risk for adverse pregnancy-related outcomes compared to non-diabetic pregnancies, but also raises new questions about an increase in fetal malformations in patients with diabetic nephropathy [12-20]. Most of the studies published so far on diabetic nephropathy during pregnancy were designed in a diabetology setting, ideal for the identification and follow-up of early diabetic nephropathy. The selection of patients referred to a nephrology unit is likely to be different and to include more complex cases or diseases other than “classic” diabetic nephropathy. Indeed, the first case followed in the newborn unit for CKD patients in 2000 was a diabetic woman, whose assisted fertilization raised a series of complex clinical and ethical issues [21].

The aim of the present study was to evaluate the outcomes recorded in cases of “severe” diabetic nephropathy in type 1 diabetic patients, referred to the nephrology unit and followed in synergy with the diabetologist. These cases were interesting because they represented a “negative selection” of type 1 diabetic patients, as only patients with severe kidney disease are referred for multidisciplinary follow-up.

## Methods

### *Study setting and inclusion criteria*

The study was performed at the Maternal-Fetal Medicine Unit of O.I.R.M., Sant’Anna University Hospital (150 beds for obstetric patients) in Turin, Italy [9, 22]. The unit’s activities are organized into various smaller units, including one dedicated to “kidney diseases in pregnancy” and one to “diabetic pregnancies”. The main baseline and outcome data in the kidney diseases unit have been gathered prospectively from the beginning of activity in 2000. The multidisciplinary team was composed of nephrologists and obstetricians [9, 22].

The first pregnancies by type 1 diabetic patients resulting in delivery were analyzed from our archive, which encompasses 12 pregnancies in 11 patients resulting in the delivery of eleven singletons and two twins. Two early spontaneous abortions were not included. The study was approved by the Ethics Committee of O.I.R.M. Sant’Anna Hospital, Ordine Mauriziano (n 335, protocol 11551/c28.2; 4/3/2011).

### Abbreviations:

AC - abdominal circumference  
BMI - body mass index  
BPD - biparietal diameter  
CC - cranial circumference  
CKD - chronic kidney disease  
CS - cesarean section  
GA - gestational age  
GFR - glomerular filtration rate  
HELLP - hemolysis, elevated liver enzymes, low platelet count (syndrome)  
K-DOQI - Kidney Disease Outcomes Quality Initiative  
LLAC - lupus-like anti-coagulant  
NICU - Neonatal Intensive Care Unit  
sCr - serum creatinine  
SGA - small for gestational age  
SPSS - Statistical Package for Social Science

### Definitions

CKD patients were stratified according to the K-DOQI guidelines [9-10, 19]. GFR calculation was based on preconception data or, in their absence, on data obtained at the first routine visit. The Cockcroft and Gault formula was chosen because it utilizes adjusted body weight to account for underweight or obesity, both of which were present in our study population. After hospitalization, creatinine clearance on 24-hour urine collection was considered to approximate GFR; proteinuria was assessed on 24-hour urine collection [9, 22].

We further used the following definitions:

1. Hypertension: systolic blood pressure  $\geq 140$  and/or diastolic blood pressure  $\geq 90$ , or anti-hypertensive therapy, even when present prior to conception [9, 22].
2. Pre-eclampsia: hypertension and proteinuria  $\geq 300$  mg/24 hours after 20 weeks of gestational age in a previously normotensive and non-proteinuric woman in the absence of other signs or symptoms indicating different nephrological diagnosis. Since the definition of “superimposed pre-eclampsia” is not unequivocal, we did not include it in this study, as previously described [9, 22].
3. Small for gestational age (SGA) newborns: birth weight below the 10<sup>th</sup> percentile according to Italian birth weight references, adjusted for gestational age [9, 22, 24].
4. Preterm delivery: delivery before 37 completed weeks of gestation (“early” delivery: before 34 completed weeks) [9, 22, 25-26].

The definition of severe diabetic nephropathy in type 1 diabetes used in our study was pragmatic:

**Table 1.** Baseline data at referral, and data at delivery from patients with type 1 diabetes followed in the nephrology unit

Case	Age at start (yr)	Referral (wk)	Delivery (wk)	sCr (mg/dl) <sup>‡</sup>	GFR (ml/min) <sup>‡*</sup>	CKD stage (K-DOQI) <sup>‡</sup>	Proteinuria (g/24 h) <sup>‡</sup>	sAlbu-min (g/dl) <sup>‡</sup>	Hb1ac (%) <sup>‡</sup>	BMI (pre)	Weight gain, kg (%)	sCr (GFR) at 3 months	Proteinuria/albumin <sup>‡</sup>
1	35	8	31	1.2-1.8	52-43	3a-3b	2.5-6.2	2.8-1.9	7.5-8.0	23.5	9 (13.4)	2.0 (45)	3/2.5
2	37	6	36	0.7-1.0	116-90	1-2	0.1-0.2	n/a	7.3-6.7	22.4	15 (23)	n/a	n/a
3	32	9	34	0.9-1.0	91-95	1-1	1.4-2.9	n/a-2.5	7.3-6.3	24.7	14 (24)	1.1 (74)	1.8/n/a
4	35	8	33	1.2-1.8	55-45	3a-3b	5.9-5.6	3.2-2.8	6.6-6.1	22	11 (20)	1.9 (40)	4/3
5 <sup>†</sup>	37	6	31	1.6-2.0	48-21	3a-4	1.8-1.9	3.8-2.9	7.3-6.5	22	9 (18)	2.1 (21)	1.5/3.1
6	30	12	34	0.6-0.7	122-142	1-1	0.1-3.1	3.9-3.0	6.4-6.5	23.7	17 (23)	0.8 (105)	0.2/3.8
7	29	9	28	1.5-5.0	66-10	2-5	6.3-17.3	3.6-1.8	11.6-6.3	20	16 (25)	4.3 (19)	5/3.1
8	31	21	31	0.5-0.7	123-133	1-1	5.4-11.8	2.8-1.8	7.2-6.2	17.9	21 (42)	0.7 (113)	1.5/4.1
9	36	5	32	1.0-1.0	68-70	2-2	0.6-4.7	4.0-2.2	12.3-6.4	21.5	12 (16)	1.0 (73)	4.8/2.9
10	35	7	32	1.2-1.5	67-57	2-3 <sup>°</sup>	0.7-9.4	4.3-2.6	6.7-6.6	18.2	8 (17)	1.9 (32)	1.3/5.7
11	40	25	34	0.9-1.0	80-64	2-2	3.1-4.4	3.3-2.8	9.0-6.7	24	14 (21)	0.9 (73)	1.4/3.5
12	34	4	34	1.1-1.5	69-66	2-2	0.2-5.7	3.7-2.5	7.0-6.8	20.3	18 (28)	1.2 (72)	1.3/1.8

**Legend:** Patient 1 underwent pancreas kidney graft 3 years after delivery. Patient 7 started dialysis one year after delivery and underwent pancreas kidney graft 2 years after delivery. <sup>‡</sup> Values are: referral-delivery. <sup>\*</sup> 24 hour urine collection. <sup>†</sup> Proteinuria (g/24 h) / albumin (g/dl) at 3 mo. <sup>°</sup> 2nd pregnancy case 4. <sup>§</sup> Twin pregnancy. *Abbreviations:* sCr - serum creatinine, GFR - glomerular filtration rate, BMI - body mass index, CKD - chronic kidney disease, K-DOQI - Kidney Disease Outcome Quality Initiative, n/a - not available.

patients referred during pregnancy from the diabetologist to the nephrologist for multidisciplinary care and patients routinely followed in the nephrology unit for diabetic nephropathy before pregnancy or for other relevant kidney diseases.

### *Prenatal and intrapartum care*

The frequency of clinical visits was tailored to patients' needs. As a rule, kidney function and proteinuria were controlled at least once a month as previously described [9, 22]. Hospitalization was required in the presence of poorly controlled hypertension, worsening of renal function, new onset or rapidly increasing proteinuria and for any potentially severe problem in mother and/or fetus [9, 22]. Indications for early delivery were:

1. Severe worsening of maternal condition before 32 weeks.
2. Severe pre-eclampsia or HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome.
3. Poorly controlled hypertension.
4. Rapid increase in nephrotic proteinuria and/or serum creatinine.

Fetal worsening included abnormal fetal heart rate tracings at any gestational age, absent end-

diastolic flow velocities in the umbilical arteries during Doppler assessment at or after 32 weeks of gestation, and no fetal growth over two weeks at later gestational ages. The main indications for admission to the Neonatal Intensive Care Unit (NICU) were: birth weight <1500 g, gestational age <34 weeks, Apgar score below 7 at 5' and need for intubation [9, 22].

### *Statistical analysis*

The main outcomes analyzed were:

- Prematurity (cut-points: 37 and 34 weeks)
- Prevalence of SGA
- Need for hospitalization in the NICU
- Proteinuria
- Kidney function
- Hospitalization
- Survival

Descriptive analyses were performed as appropriate (mean and standard deviation for parametric and median and range for non-parametric data). Because of the high heterogeneity of both diabetic cases followed in the diabetes unit and of CKD patients, no attempt was made to identify a control group and the analysis is merely descriptive (SPSS version 18.0 for Windows).

**Table 2.** End-organ involvement in patients with type 1 diabetes followed in the nephrology unit

Case	Diabetes onset (age)	Diabetes duration (yr)	Retinopathy	Kidney disease	Clinical neuropathy	Hypertension: prior - at referral - at delivery	Other
1	12	24	Laser-treated	Biopsy: >50% sclerosis	No	Y-Y-Y	Assisted fertilization
2	11	27	Laser-treated	Biopsy: >30% sclerosis	No	N-N-N	Hypothyroid (autoimmune)
3	6	26	Laser; hemorrhage in pregnancy	Overt nephropathy	Yes (peripheral)	Y-Y-Y	
4	17	18(1st pregnancy)	Laser-treated	Biopsy: >40% sclerosis	Yes (visceral)	Y-N-Y	Mionecrosis
5	17	21(2nd pregnancy)	Laser-treated	Biopsy: >40% sclerosis	Yes (visceral)	Y-N-Y	Mionecrosis
6	11	20	Blind	Renal tuberculosis	Yes (both)	N-N-Y	
7	15	15	Laser in pregnancy	Overt nephropathy	No	Y-Y-Y	
8*	11	21	Laser-treated	Nephrotic syndrome in pregnancy	No	N-N-Y	Thyroiditis in pregnancy
9	10	26	Laser-treated	Previous nephrotic syndrome	No	Y-N-Y	Hypothyroid (autoimmune) alopecia
10	10	25	Laser-treated	Overt nephropathy	No	Y-N-Y	Previous pre-eclampsia
11	14	27	Laser-treated	Overt nephropathy	Yes (peripheral)	N-N-Y	Hypothyroid (autoimmune)
12	14	21	Laser-treated	Overt nephropathy	Yes (peripheral and demyelizing)	Y-Y-Y	LLAC positive

**Legend:** \* Twin pregnancy. LLAC - lupus-like anti-coagulant, Y - yes, N - no.

## Results

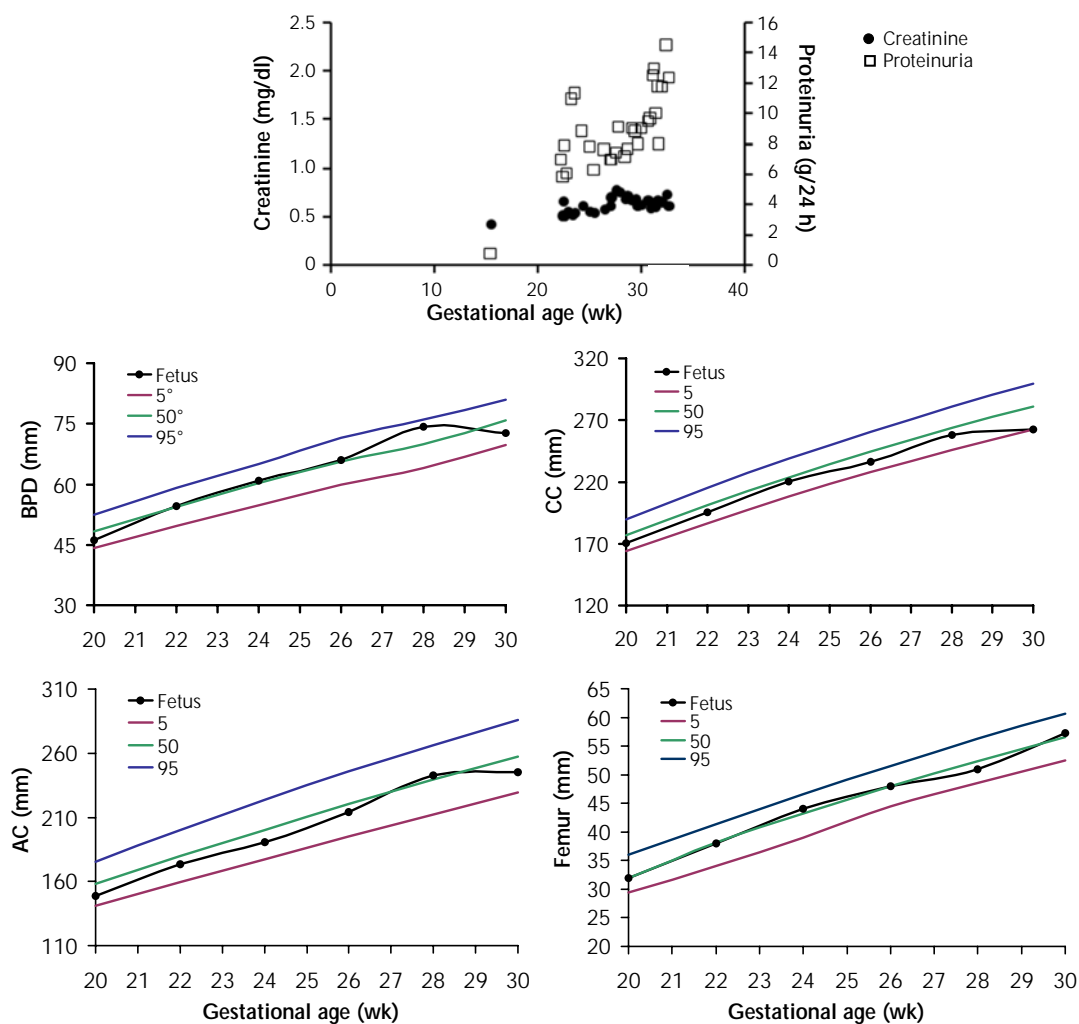
### Baseline data

In the study period (January 2000 to December 2012), 383 pregnancies were referred to the unit dedicated to kidney diseases in pregnancy (338 patients). The overall prevalence of pregnancies with type 1 diabetes was 3.65%. The main clinical features of the 11 diabetic patients (12 pregnancies) included in the study are reported in **Table 1**.

As expected, end-organ damage was also present in all "severe kidney disease" cases, with laser-treated retinopathy being the rule. Noticeably, 4/11 patients had thyroid diseases and two patients presented with other autoimmune disorders (lupus anticoagulant positive and autoimmune alopecia); clinically evident neuropathy was present in half of the cases (**Tables 1-2**). Three patients underwent kidney biopsy, which resulted in a diagnosis of diabetic nephropathy. It is noteworthy

that the involvement of over 30% of the glomeruli in patient 2 was associated with normal kidney function without significant increase in albuminuria throughout pregnancy. Only one patient had another kidney disease at referral (previous renal tuberculosis, in the context of severe microvascular damage as bilateral blindness caused by diabetic nephropathy testified).

The baseline conditions were scattered. Four patients were in stage 1 CKD. Median GFR at referral was 67 ml/min (48-122.6) and proteinuria 1.6 g/day (0.1-6.3 g/day). One patient was less than 30 years old at the beginning of pregnancy (median age 35 (29-40) years), in line with a long duration of diabetes (median duration 21 (15-27) years) (**Table 1**). Most of the patients were referred early during pregnancy, except for case 8 (twin pregnancy), who developed an acute-onset nephrotic syndrome during mid-pregnancy (**Figure 1, Table 2**), and case 11 who was transferred for nephrotic proteinuria development.



**Figure 1.** The patterns of proteinuria and fetal growth in patient #8 (twin pregnancy). The diagrams show a sudden increase in proteinuria and a progressive difference in the development of the two fetuses. The male fetus was affected by great vessel transposition and died after cardiac surgery 6 days after birth. *Abbreviations:* BPD - biparietal diameter, AC - abdominal circumference, CC - cardiac circumference.

### Maternal and fetal outcomes

**Tables 3** and **4** report the main maternal and fetal outcomes. Eleven pregnancies developed severe proteinuria, nine of which were in the full-blown nephrotic range. One patient only (case 2, with biopsy-proven diabetic nephropathy) did not develop significant proteinuria during pregnancy (**Table 1**). The pattern of proteinuria during pregnancy was characterized by a sharp or a stepwise increase, as shown in **Figures 2-3** (cases 9-10: stepwise increase of proteinuria in pregnancy),

and in **Figure 4** (sudden increase of proteinuria during late pregnancy). In contrast, an increase in serum creatinine was not always present and only one patient, who started dialysis one year later and received a kidney-pancreas graft two years after delivery, shifted by two CKD stages during pregnancy (case 8).

As for blood pressure, all but one patient became hypertensive at delivery, while blood pressure normalized in early pregnancy in 4 patients, but required antihypertensive medication thereafter (**Tables 2** and **4**). Good diabetes control

**Table 3.** Main fetal outcome

Case	GA at delivery	Delivery	Main indication to delivery	Gender of child	Weight (g)	Percentile	Apgar (1-5 min)	Hospitalization mother (days)	Days in NICU	Follow-up of the child (yr)
1	31	V	Spontaneous labor	M	1590	10-50	7-8	132	24	10.25
2	36	CS	Cardiotocographic alterations	F	2360	10-50	5-9	10	0	2**
3	34	CS	Increase in proteinuria	F	2160	10-50	6-8	8	4	1**
4	33	CS	Increase in proteinuria	F	1980	10-50	9-9	73	15	7.17
5	31	CS	Increase in proteinuria	M	1970	50-90	8-8	47	21	4.17
6	34	CS	Increase in proteinuria and blood pressure	M	2970	50-90	7-7	20	7	3.75
7	28	CS	Kidney function impairment	F	935	10-50	7-8	92	77	3.00
8*	31	CS	PROM and spontaneous labor	M	1270	< 5°	4-7	85	6	0.50 <sup>†</sup>
				F	1275	10-50	7-8		6	1.17
9	32	CS	Cardiotocographic alterations, increase in proteinuria	F	1920	50-90	6-8	29	15	0.83
10	32	CS	Increase in proteinuria and of serum creatinine	F	1550	10-50	8-8	23	40	0.50
11	34	V	Spontaneous labor	F	2350	50-90	7-8	24	18	0.33
12	34	V	Spontaneous labor	F	2620	90	8-9	15	7	0.25

**Legend:** Malformations: great vessel transposition in the male twin child (case 8); emivertebra in the female child (case 11). *Abbreviations:* GA - gestational age, CS - cesarean section, M - male, F - female, NICU - neonatal intensive care unit, V - vaginal. \* Twin pregnancy. \*\* Lost to follow up after the period indicated. <sup>†</sup> Died after 6 mo.

was obtained in most cases, with an improvement compared to the baseline data at referral; 11/12 cases attained a glycated hemoglobin level of less than 7% at delivery (**Table 1**).

Pre-term delivery was the rule in this cohort and seven pregnancies were at “early pre-term” gestational age (<34 weeks). Only the male twin (case 8) was an SGA baby, while all the others were above the 10<sup>th</sup> centile. These findings are a combination of spontaneous pre-term deliveries (cases 1, 8, 11, 12) and induced deliveries because of maternal (cases 3-7, 10) or fetal problems (cases 2 and 9), thus avoiding intrauterine growth restriction and SGA development. Despite prematurity, all the singletons were developing normally and attaining the expected age-adjusted goals at the last update (two cases were lost to follow-up 1-2 years after delivery). The male twin child died at 6 days of life from cerebral hemorrhage following cardiac surgery (**Table 3**).

### Therapeutic approaches

The therapeutic approach was tailored and based upon support therapy (**Table 4**). Support therapy included strict diabetic control by means

of either multi-injective therapy or microinfusion, and strict blood pressure control with a goal of 120-130 systolic and less than 80 diastolic, with combined use of alpha-methyldopa (first choice) and nifedipine (second choice, for the side effect of increasing proteinuria). Doxazosin was employed only in cases of intolerance to other drugs. Acetyl salicylate was employed in 10/12 pregnancies from early pregnancy onwards, on the hypothesis of favoring placentation. Two cases were excluded from acetyl salicylate treatment because of severe florid retinopathy (**Table 4**).

In the first cases followed by our unit, when our experience was limited, patients were hospitalized for longer periods, thus allowing strict clinical fetal-maternal surveillance. In particular, we performed rapid adjustments of diabetes control or of anti-hypertensive drugs. In the most recent pregnancies, with the exception of the twin pregnancy, hospitalizations were considerably shortened and patients were monitored at least once a week in the outpatient clinic. Bed rest was prescribed in all cases involving nephrotic proteinuria. A moderately protein-restricted diet was employed in cases with severe proteinuria and/or kidney function im-

**Table 4.** Main therapeutic approaches during pregnancy

Case	Diet	Insulin	Anti-hypertensive agents	Acetilsalicylate	Other
1	Vegan, supplemented	4/day	Doxazosine	Yes	
2	None	4/day	None	No	Levotyroxine
3	None	4/day	Niphedipine	No**	
4	Vegan, supplemented	microinfusion	$\alpha$ -metildopa	Yes	
5	Vegan, supplemented	microinfusion	$\alpha$ -metildopa	Yes	
6	None	4/day	Doxazosine	Yes	Levotyroxine
7	Vegan, supplemented	microinfusion	Niphedipine, $\alpha$ -metildopa	No <sup>†</sup>	
8*	Vegan, supplemented	microinfusion	$\alpha$ -metildopa	Yes	
9	Vegan, supplemented	microinfusion	$\alpha$ -metildopa	Yes	Levotyroxine, alprazolam, paroxetina
10	Vegan, supplemented	5/day, microinfusion, 5/day	$\alpha$ -metildopa, niphedipine	Yes	
11	Vegan, supplemented	microinfusion	Niphedipine	Yes	Levotyroxine
12	Vegan, non-supplemented	4/day	Niphedipine, $\alpha$ -metildopa	Yes	

**Legend:**\* Twin pregnancy. \*\* Severe retinopathy with hemorrhage. <sup>†</sup> Laser treatment in pregnancy.

pairment to reduce pregnancy-, diabetes- and nephritic syndrome-related hyperfiltration, (0.6-0.8 g/kg/day proteins, in association with keto acid and amino acid supplementation) [27].

## Discussion

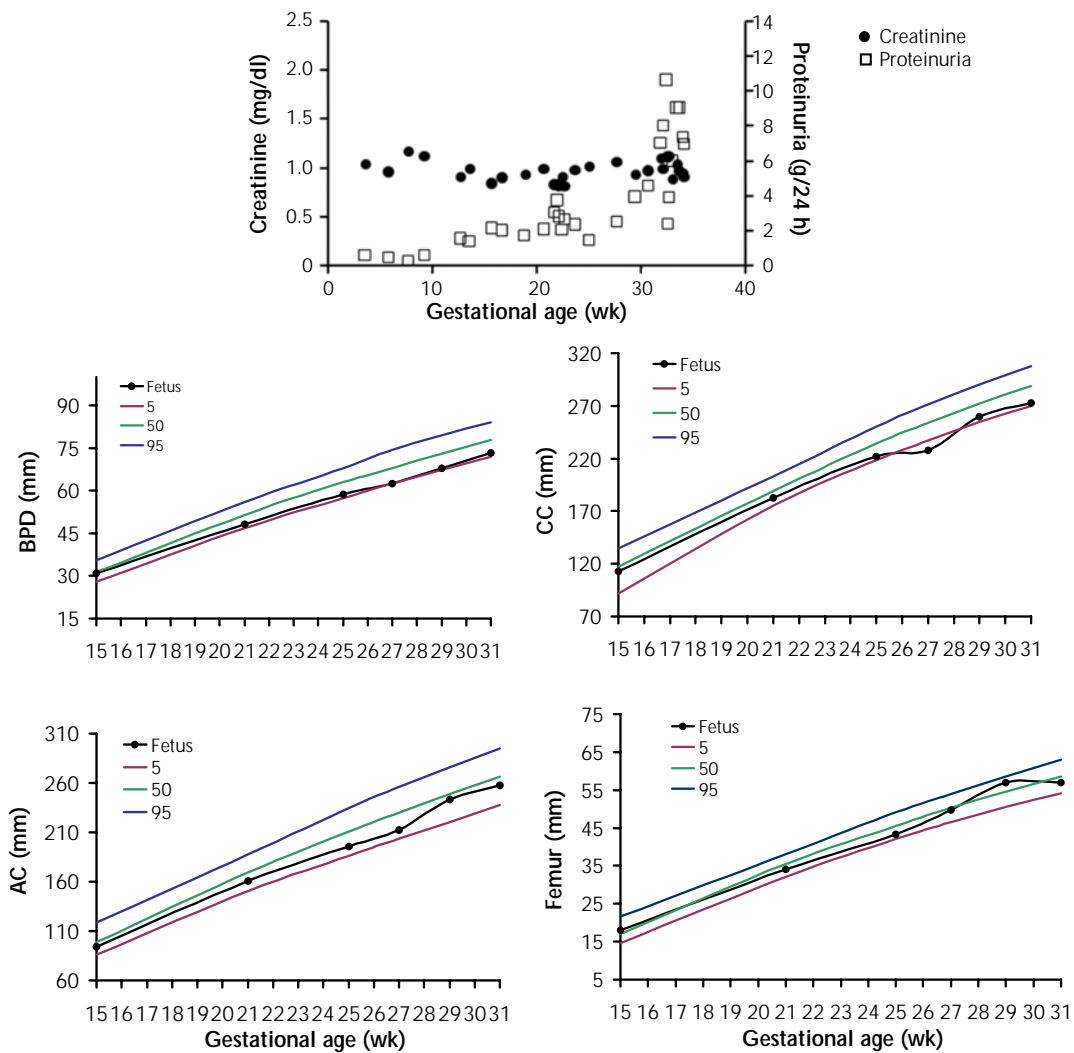
The aim of the present study was to analyze our clinical experience with the follow-up of a small, albeit complex, series of patients with severe diabetic nephropathy during pregnancy. This combination of two high-risk situations was analyzed for the purposes of better characterization of the risks as a guide for improved treatment. Despite the small number of cases, there are three major findings which may contribute to the current literature, partly in line with previous reports.

Firstly, type 1 diabetic patients may abruptly develop nephrotic proteinuria in pregnancy, with a very unusual pattern outside of pregnancy, reminiscent of other primary glomerular diseases (**Figures 1-4, Tables 1-2**). This observation was reported over 20 years ago and has received little attention since then [28]. The lack of correlation of proteinuria with hypertension and normal fetal growth (only one twin child was classified as SGA) opposes the simplistic interpretation of this picture

as “pre-eclampsia” (**Figures 1-4**). While only kidney biopsy could exclude a concomitant disease other than diabetic nephropathy, the slow decrease in proteinuria after delivery is neither typical of pre-eclampsia nor of the related, ill-defined “pregnancy-induced proteinuria” (by definition the return to baseline should be completed in 1-3 months), nor of other primary glomerular diseases (usually progressive). Such a pattern may fit the interpretation of a slowly resolving effect of hyperfiltration against a background of diabetic nephropathy [26, 28]. Whatever the case, the sudden development of or increase in proteinuria should be kept in mind, particularly as severe proteinuria may merge into the diagnosis of severe pre-eclampsia, therapy of which is timed delivery [26, 28, 29-30].

The second point is the importance of prematurity. All our patients delivered before term, in the majority of cases at 34 weeks or earlier. Indeed, the role of spontaneous labor, the cause of early delivery in one third of the cases, presents a challenge which should probably be borne in mind when planning surveillance of the third trimester of pregnancy (**Tables 1-3**).

The third point regards materno-fetal care: only one patient in our high-risk group experienced a



**Figure 2.** Proteinuria, serum creatinine, and fetal growth in case 9. The figure shows the stepwise increase in proteinuria during pregnancy and the normal fetal development. *Abbreviations:* BPD - biparietal diameter, AC - abdominal circumference, CC - cardiac circumference.

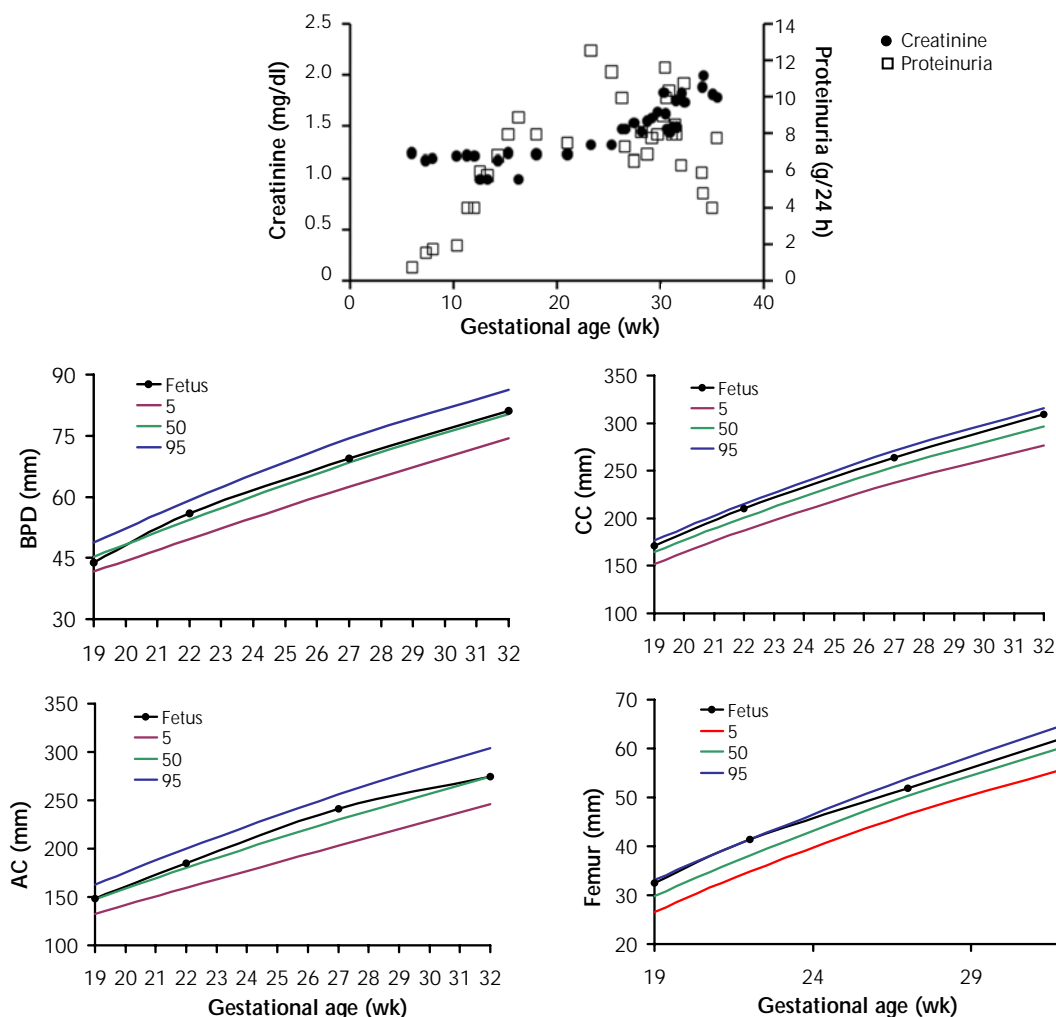
rapid and non-reversible rise in serum creatinine, thus requiring dialysis one year after delivery, followed by pancreas-kidney transplantation (**Table 1**). Within the limits of a small case series, our observations may be in favor of a tailored policy of “kidney rest”. All the available tools must be employed to reduce hyperfiltration, including strict diabetes and blood pressure control, bed rest and cautious use of moderate protein restriction [27].

Despite prematurity and in line with the feasibility of moderate protein restriction during preg-

nancy, all singletons were appropriate for gestational age and all had attained normal developmental goals after delivery at the last available follow-up (**Table 3**). The male twin, who was the only SGA baby and who was affected by great vessel transposition, died 6 days after birth, which is due to the remarkably higher risks of twin pregnancies in CKD patients [31].

Our study has several limitations, shared by most series of highly selected cases: the single center analysis, the small number of cases described,





**Figure 3. Proteinuria, serum creatinine and fetal growth in case 10.** The figure shows the stepwise increase of proteinuria in pregnancy and the normal fetal development. *Abbreviations:* BPD - biparietal diameter, AC - abdominal circumference, CC - cardiac circumference.

and the lack of control groups. Furthermore, in dealing with type 1 diabetes patients it does not consider the two emerging categories of diabetes in pregnancy: gestational diabetes and type 2 diabetes mellitus [32-35]. However, within these obvious limitations, it is one of few studies describing patients with “severe” diabetic nephropathy referred to nephrological healthcare. It offers some insight into the clinical management of these difficult patients, and suggests that particular attention should be paid to the development of severe and sudden-onset proteinuria and the occurrence of early pre-term labor.

## Conclusions

This study, which aimed to assess materno-fetal outcomes in a small series of pregnancies in type 1 diabetic patients with diabetic nephropathy, underlines the importance of further investigation to address the mechanisms underlying the sudden development of/increase in proteinuria and the reasons for early spontaneous labor. The promising results obtained by strict metabolic and clinical surveillance and by the few available means for reducing hyperfiltration (diabetes and blood pressure control, together with bed rest and a moder-

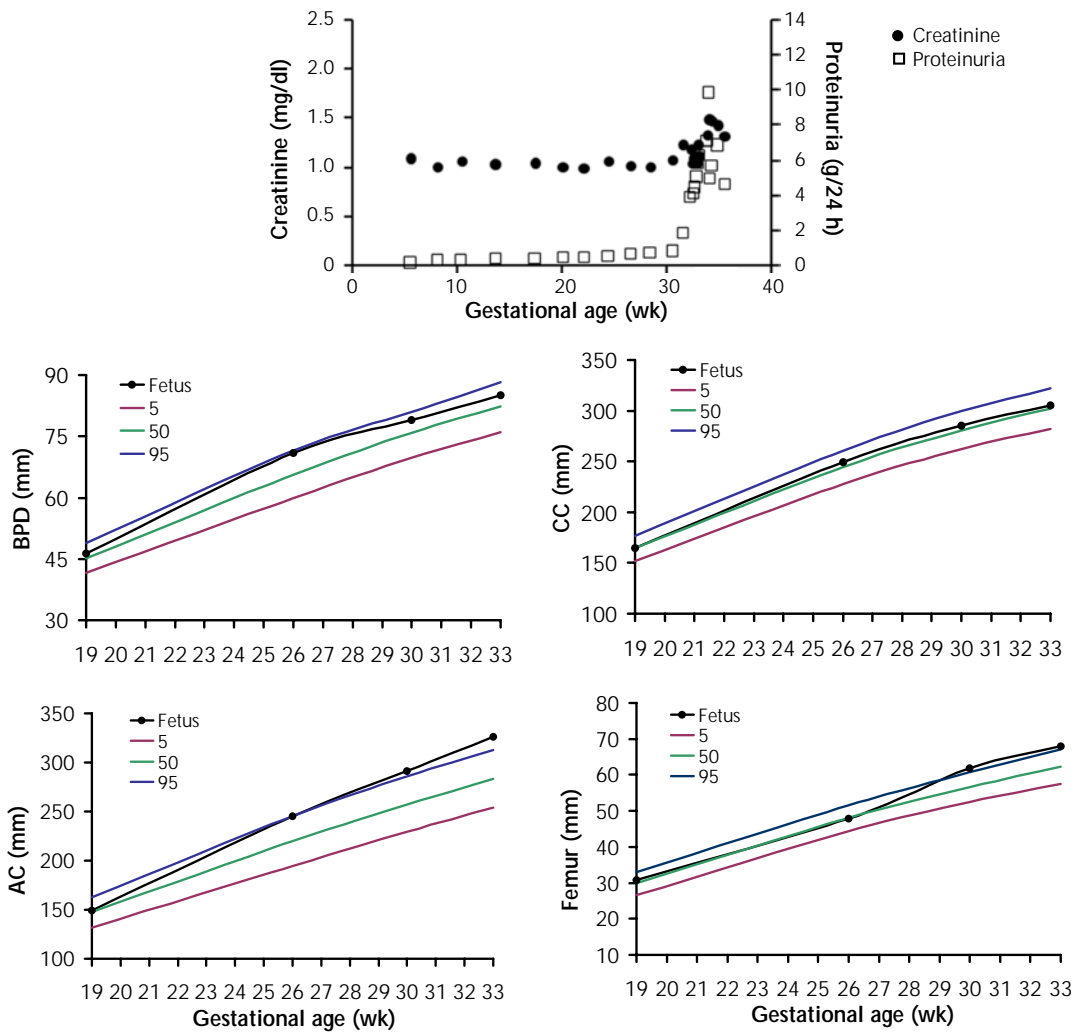


Figure 4. Proteinuria, serum creatinine and fetal growth in case 11. The figure shows a the sudden increase of proteinuria in the late phase of pregnancy. *Abbreviations:* BPD - biparietal diameter, AC - abdominal circumference, CC - cardiac circumference.

ate reduction in protein intake) need confirmation on a larger scale.

**Disclosure:** The authors declare no conflict of interests.

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