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# Excessive urinary tract dilatation and proteinuria in pregnancy: a common and overlooked association?

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## Abstract

**Background:** Proteinuria and dilatation of the urinary tract are both relatively common in pregnancy, the latter with a spectrum of symptoms, from none to severe pain and infection. Proteinuria is a rare occurrence in acute obstructive nephropathy; it has been reported in pregnancy, where it may pose a challenging differential diagnosis with pre-eclampsia.

The aim of the present study is to report on the incidence of proteinuria ( $\geq 0.3$ ;  $\geq 0.5$  g/day) in association with symptomatic-severe urinary tract dilatation in pregnancy.

**Methods:** Case series. Setting: Nephrological-Obstetric Unit dedicated to pregnancy and kidney diseases (January 2000-April 2011). Source: database prospectively updated since the start of the Unit. Retrospective review of clinical charts identified as relevant on the database, by a nephrologist and an obstetrician.

**Results:** From January 2000 to April 2011, 262 pregnancies were referred. Urinary tract dilatation with or without infection was the main cause of referral in 26 cases (predominantly monolateral in 19 cases): 23 singletons, 1 lost to follow-up, 1 twin and 1 triplet. Patients were referred for urinary tract infection (15 cases) and/or renal pain (10 cases); 6 patients were treated by urologic interventions ("JJ" stenting). Among them, 11 singletons and 1 triple pregnancy developed proteinuria  $\geq 0.3$  g/day (46.1%). Proteinuria was  $\geq 0.5$  g/day in 6 singletons (23.1%). Proteinuria resolved after delivery in all cases. No patient developed hypertension; in none was an alternative cause of proteinuria evident. No significant demographic difference was observed in patients with renal dilatation who developed proteinuria versus those who did not. An association with the presence of "JJ" stenting was present (5/6 cases with proteinuria  $\geq 0.5$  g/day), which may reflect both severer obstruction and a role for vesico-ureteral reflux, induced by the stent.

**Conclusions:** Symptomatic urinary tract dilatation may be associated with proteinuria in pregnancy. This association should be kept in mind in the differential diagnosis with other causes of proteinuria in pregnancy, including pre-eclampsia.

## Background

Dilatation of the urinary tract is common in pregnancy in particular in the last trimester [1-4]. The cause of the dilatation is disputed, some advocating hormonal effects and others obstruction. There is a broad spectrum of this 'syndrome', some women may be completely asymptomatic, others have only transient mild loin pain while

other patients experience recurrent episodes of severe loin pain and/or lower abdominal pain; very occasionally these anatomical changes can be exaggerated with massive ureteral and renal pelvis distension (as well as slight reduction in renal cortical width) and very rarely, the changes may be extreme and precipitate a so-called "over-distension syndrome" even with reversible acute renal failure [5-7].

In general, dilatation on the right side is more common and more pronounced, being reported, in a mild form, usually involving calices only, in up to 90% of the

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pregnancies in the last gestational weeks. Near term, mild urinary dilatation tends to become bilateral, in keeping with the theory that it is caused by compression by the iliac arteries where the latter cross the true bony pelvis [8].

On the right side, dilatation is usually considered as presumably related to pregnancy, while dilatation on the left side, especially if unilateral, is probably related to a different situation and is less likely to resolve after delivery [5-8].

The possibility that urinary tract obstruction may occasionally cause proteinuria outside of pregnancy is well known, even if not frequently reported [9-11]; its degree is usually sub-nephrotic and its pathogenesis is usually related to increased pressure in the renal pelvis, leading to a diuretic response from the contralateral kidney. Proteinuria caused by kidney obstruction is usually mild and considered of tubular origin, although different mechanisms may be operating [12,13]. Very few cases of massive proteinuria in the context of unilateral renal dilatation have been reported. Notably, a relatively recent report dealt with a pregnant patient who developed nephrotic proteinuria. In this very well documented case, proteinuria was found to stem from both kidneys at the time of laparoscopic intervention and resolved after pyeloplasty performed a few months after delivery [14]. The authors of the report stated that the lack of proteinuria prior to pregnancy and the failure to resolve after delivery pointed to pregnancy as a catalyst in the development of proteinuria [14]. A few interesting cases had been reported, in which urinary tract dilatation was presumably the cause of severe pre-eclampsia or of kidney function impairment [15,16]. However, according to a Medline search at June 2011 (combining the terms proteinuria, hydronephrosis, kidney and dilatation with pregnancy), we could locate no surveys of the prevalence of proteinuria associated with urinary tract dilatation in pregnancy in the last decade, with the exception of the case mentioned above.

This issue is however of great interest, particularly with respect to the differential diagnosis with pre-eclampsia and other causes of pregnancy-induced proteinuria, including a vast array of chronic kidney diseases.

We therefore evaluated whether or not proteinuria without obvious cause was present in 26 pregnant women, referred to our specialty clinic with excessive and/or symptomatic urinary tract dilatation in pregnancy, with or without sign of upper urinary tract infection.

## Methods

### Study setting

The study was performed in the Maternal-Foetal Unit of the University Hospital OIRM S. Anna, Turin, Italy, where all pregnant patients with kidney diseases have

been followed by the same obstetric and nephrological team since 2000. A large database had been structured and data were prospectively gathered since the start of the activity [17].

From January 2000 to April 30<sup>th</sup> 2011, 262 pregnancies were observed in 235 women referred to our Unit dedicated to pregnancy and kidney diseases. Twenty-six of the patients (26 patients; 26 pregnancies) displayed excessive (above 3 cm) and/or symptomatic urinary tract dilatation (10% of the overall referred population) as a main clinical problem and reason for referral. The present analysis is focused on this cohort.

### Diagnostic and follow-up policies. Main definitions

The diagnostic work-up for patients with signs or symptoms of kidney disease referred to the Unit includes renal function assessment (at the first visit in the Unit: creatinine and proteinuria on 24-hour urine collection) and immunological and coagulation screening. Abdominal ultrasounds are performed at least once in all cases; they are routinely performed in the same two settings (Materno-Foetal Hospital and S Luigi Hospital) by a small group of skilled operators.

In the case of known urological problems preceding pregnancy, the follow-up policy includes urinalysis and urinary cultures every week, or on alternate weeks, as well as ultrasounds at least every three months, and more frequently in the case of urinary tract dilatation. Since the entity of the urinary tract dilatation is also dependent upon hydration and position, a clear cut-off between physiological and pathological was not available from the literature; for the present study, we considered as "excessive" the urinary tract dilatation when exceeding 3 cm of maximal diameter, or over 2 cm when symptomatic [1,6-8,18,19]. The dilatation was considered as symptomatic when accompanied by flank pain, enhanced by palpation, and or by signs of upper urinary tract infection.

Due to the risks of any invasive manoeuvre in pregnancy, positioning of "JJ stents" is limited to cases with severe dilatation, untreatable pain and/or evidence of complete or almost complete obstruction and infection.

Hypertension is defined as systolic blood pressure  $\geq 140$  and/or diastolic blood pressure  $\geq 90$ , or anti-hypertensive therapy. In the case of hypertension, 24-hour blood pressure monitoring and echocardiography are performed; other analyses are prescribed on demand. CKD is classified according to K-DOQI guidelines, using pre-pregnancy data whenever possible. When these are not available, data at referral are used. The Cockcroft-Gault and EPI formulae (based upon the first available serum creatinine data) and 24-hour urine assessments (for the subsequent measurements) are routinely employed for the

patients with CKD stages 2–5. For other details on definitions, please refer to our previous study [17].

The frequency of nephrological and obstetric controls is individualized, weekly to monthly. In addition to the routine pregnancy controls, creatinine clearance on 24 hour urine collection is routinely required at referral; all patients undergo (at least) a monthly determination of serum creatinine and dipstick proteinuria, uric acid, urinalysis and urinary culture, serum electrolytes, coagulation and blood cell counts. If proteinuria is present, 24-hour urine collection is requested. Other tests are required on demand. Proteinuria is classified into tubular pattern (exclusive or prevalent: Beta 2 microglobulin, alfa 2 microglobulin, lysozyme), glomerular pattern (exclusive or prevalent: albumin, transferrin, IgG), and mixed pattern.

Ultrasound biometry and Doppler velocimetry of uterine and umbilical arteries are individualized (every two-four weeks if there is a risk of foetal growth restriction).

Hospitalization is required in the presence of uncontrolled or new-onset hypertension, worsening of renal function, new onset or worsening of proteinuria, or any intercurrent problem of mother and/or foetus (abnormal foetal growth and/or severely abnormal umbilical Doppler) [17].

Preterm delivery is defined as delivery before 37 completed weeks of gestation; “early pre-term” delivery is defined as delivery before the 34<sup>th</sup> completed gestational week. Caesarean section is performed for foetal indications or in cases of unfavourable conditions for, or lack of response to, induction. Apgar scores are recorded at 1 and 5 min by the neonatologists. A newborn is defined as Small for Gestational Age (SGA) when the birth weight is below the 10<sup>th</sup> centile according to Italian birth weight references [17].

#### **Patient selection**

The patients were selected from the Unit’s database according to the following criteria: symptomatic or severe urinary tract dilatation at ultrasounds performed at any time during pregnancy; availability of at least one full functional evaluation with 24-hour proteinuria. In all cases, at least 2 controls of 24-hour proteinuria were available. Patients referred for acute upper urinary tract infection who did not display renal dilatation at ultrasounds were selected as a control group (14 cases, from the 262 pregnancies referred). After the initial selection, the clinical charts of all patients were reviewed by the same operators.

As the definition of “significant” proteinuria may be controversial, and some Authors stress the potential overlap between normal and pathological data, setting the limit at 0.3 g/day, two cut-points were tested: 0.3 and 0.5 g/day. In the patients who had developed

proteinuria  $\geq 0.5$  g/day, post-pregnancy data were obtained from the clinical charts or by phone inquiry.

#### **Ethical approval and consent to the study**

The overall research and build-up of the archives of the patients followed in our Unit, focused on the differential diagnosis between pre-eclampsia and CKD and on the risks of CKD in pregnancy was approved by the Ethical committee of the OIRM-S. Anna Hospital of the University of Turin (number 335; protocol 11551/c28.2; data of final approval 4.3.2011); since the start of the activity, all patients followed in the Unit signed an informed consent for the use of anonymous data for research purposes. Specific consent was requested to the patient whose image is reported in the present paper.

#### **Statistical analysis**

A descriptive analysis was performed as appropriate. The patients with renal dilatation and proteinuria were compared with the cases without proteinuria by Chi square test (discrete variables) and Student’s t-test (continuous variables). For non parametric comparisons, Mann Whitney test was employed.

#### **Results**

##### **Prevalence of proteinuria in pregnant patients with urinary tract dilatation**

In the study period (January 2000 - April 2011), 262 pregnancies in 235 women were referred to the Outpatient Unit for Kidney Diseases in Pregnancy. Symptomatic or excessive urinary tract dilatation was the main sign in 26 cases (10% of pregnancies): 23 singletons, 1 lost to follow-up, one twin, one triple pregnancy. Dilatation was predominantly monolateral in 19 cases.

The overall prevalence of proteinuria  $\geq 0.3$  g/day (the threshold level for the differential diagnosis with pre-eclampsia) associated with urinary tract dilatation was high: 11 singletons and 1 triple pregnancy developed proteinuria before term (46.1% of the overall population; 48% of the singletons, not considering the patient lost to follow-up).

Proteinuria was  $\geq 0.5$  g/day in 7 cases, namely 6 singletons and one triple pregnancy (26.9%).

Patients were mainly referred for upper urinary tract infection (15 cases) and/or renal pain (10 cases). In 4 cases, the finding of urinary tract dilatation exceeding 3 cm was incidental during an evaluation of kidney ultrasounds.

Six patients (5 of them in the higher proteinuria group) were treated by urologic interventions (“JJ” stenting), 4 in our institution and 2 in a different setting, before referral to our Unit.

### Characteristics of the patients with and without proteinuria

The main clinical and biochemical data of the patients with and without proteinuria (cutpoint at  $\geq 0.3$  g/day and  $\geq 0.5$  g/day) associated with urinary tract dilatation are reported in Table 1.

Due to the lack of referral data as for incidence of low-grade proteinuria in multiple pregnancies, only singletons are reported. One patient dropped out from

follow-up before delivery, and was likewise excluded, thus leaving 23 cases for the statistical analysis.

No significant baseline difference was observed in patients with renal dilatation who developed proteinuria versus those who did not, nor in the cohort of patients referred for upper urinary tract infection without proteinuria (Table 1). Proteinuria always resolved after delivery and after stent removal, routinely performed within one month after delivery in all but one patient, in

**Table 1 Prevalence and main characteristics of patients, according to the presence of proteinuria, dilatation or infection (data at referral and delivery)**

|  | Patients with urinary tract dilatation and proteinuria <0.3 g/day (12 pts) | Patients with urinary tract dilatation and proteinuria $\geq 0.3$ <0.5 g/day (5 pts) | Patients with urinary tract dilatation and proteinuria $\geq 0.5$ g/day (6 pts) | Patients with acute urinary tract infection without dilatation (14 pts) |
|--|--|--|---|---|
| Mean age (start of pregnancy) $\pm$ sd | 28.6 $\pm$ 5.93  | 29.2 $\pm$ 5.93  | 29.8 $\pm$ 4.49   | 29.8 $\pm$ 6.60   |
| Primiparous n (%)                      | 5 (41.7%)  | 3 (60%)  | 2 (33.3%)   | 9 (64.3%)   |
| Median week of referral                | 23 (4–36)  | 8 (5–33)   | 30 (18–35)  | 21 (7–36)   |
| <b>Data at referral of pregnancy</b>   |  |  |   |   |
| Mean creatinine (mg/dl) $\pm$ sd       | 0.6 $\pm$ 0.12   | 0.7 $\pm$ 0.09   | 0.6 $\pm$ 0.21  | 0.6 $\pm$ 0.13  |
| GFR (EPI)                              | 124 $\pm$ 13   | 118 $\pm$ 12   | 125 $\pm$ 25  | 120 $\pm$ 14  |
| Hypertension                           | No   | No   | No  | No  |
| Median proteinuria (g/24 h) *          | 0.1 (0.08-0.31)  | 0.1 (0.07-0.18)  | 1.09 (0.1-2.65)   | 0.1 (0.06-0.53)   |
| “JJ” stenting during pregnancy §       | 0  | 1/5  | 5/6   | 0   |
| <b>Data at delivery</b>                |  |  |   |   |
| Mean creatinine (mg/dl) $\pm$ sd       | 0.6 $\pm$ 0.15   | 0.6 $\pm$ 0.20   | 0.7 $\pm$ 0.22  | 0.6 $\pm$ 0.12  |
| GFR                                    | 124 $\pm$ 18   | 118 $\pm$ 26   | 118 $\pm$ 27  | 117 $\pm$ 14  |
| Hypertension                           | No   | No   | No  | 1 (7.1%)  |
| median proteinuria (g/24 h) **         | 0.1 (0.07-0.16)  | 0.3 (0.3-0.38)   | 1.7 (0.6-2.54)  | 0.1 (0.1-0.23)  |
| Mean gestational age $\pm$ sd ***      | 38.8 $\pm$ 1.7   | 38.6 $\pm$ 1.8   | 35.5 $\pm$ 1.8  | 38.8 $\pm$ 1.4  |
| Preterm delivery <37 weeks n (%)§§     | 2 (16.7%)  | 0  | 4 (66.7%)   | 0   |
| Vaginal delivery n (%)                 | 10 (83.3%)   | 2 (40%)  | 6 (100%)  | 12 (85.7%)  |
| Weight of newborn $\pm$ sd ****        | 3315.4 $\pm$ 548.92  | 3136 $\pm$ 453.02  | 2553.3 $\pm$ 372.86   | 3236.7 $\pm$ 494.7  |
| Newborns $\leq 10^{\text{th}}$ centile | 0  | 0  | 1 (16.7%)   | 1 (7.1%)  |

Note: Singletons only; one twin and one triplet pregnancies in the group with dilatation were not considered. One further patient dropped out from follow-up before delivery (also excluded).

All patients underwent at least two measurements of proteinuria on 24 hour urine collections.

\* Mann–Whitney test: group 3 versus 1:  $p = 0.002$ ; versus 2:  $p = 0.019$ ; versus 4  $p = 0.012$ .

\*\* Mann–Whitney test: group 3 versus 1:  $p = 0.000$ ; versus 2:  $p = 0.005$ ; versus 4  $p = 0.000$ .

\*\*\* T student test: group 3 versus 1:  $p = 0.0016$ ; versus 2:  $p = 0.0184$ ; versus 4  $p = 0.0003$ .

\*\*\*\* T student test: group 3 versus 1:  $p = 0.0077$ ; versus 2:  $p = 0.0437$ ; versus 4  $p = 0.0074$ .

§ Chi square test: group 3 versus 1:  $p = 0.0016$ ; versus 2:  $p = 0.1356$ ; versus 4  $p = 0.0007$ .

§§ Chi square test: group 3 versus 1:  $p = 0.1160$ ; versus 2:  $p = 0.0971$ ; versus 4  $p = 0.0050$ .

Singletons only.

whom proteinuria tested negative at 3 months. No patient developed hypertension during pregnancy or in the first month after delivery; no alternative cause of proteinuria was evident. In keeping with the absence of other pathological conditions, delivery was vaginal in the vast majority of the cases in all subsets considered (against a background of 25% caesarean deliveries in low-risk pregnancies in our Unit [17]).

With regard to outcomes, patients with higher levels of proteinuria displayed significantly greater morbidity than those without proteinuria: delivery was preterm in 4/6 cases and thus a significantly lower birth weight was recorded (Table 1).

Interestingly, there was a strong association with the positioning of JJ stenting and proteinuria, as stenting

had been performed in 5 cases with excessive renal dilatation and proteinuria and in only one case in the low-proteinuria group (Table 1).

#### Characteristics of patients with proteinuria $\geq 0.5$ g/day

The main clinical features and outcomes of singletons with proteinuria equal or above 0.5 g/day are summarised in Table 2. Only one patient (case 2) had a history of stone disease, although previously undetected kidney stones were found at ultrasounds in 3/5 cases. One patient had a history of urinary tract involvement, with colicky pain during a previous pregnancy. All patients had normal renal function throughout pregnancy and no ultrasound evidence of any condition predisposing to proteinuria or otherwise indicating “chronic kidney disease” (such as

**Table 2 Main reasons for referral and main clinical characteristics in singletons with  $\geq 0.5$  g/proteinuria/day and renal dilatation**

|  | Case 1   | Case 2   | Case 3           | Case 4   | Case 5  | Case 6  |
|--|--|--|------------------|--|---|---|
| Age (start of pregnancy)                   | 24   | 34   | 27               | 27   | 30  | 36  |
| Weight (start of pregnancy) – Kg           | 68   | 59   | 64               | 55   | 65  | 50  |
| BMI (start of pregnancy) Kg/m <sup>2</sup> | 22.5   | 21.1   | 23.5             | 21.5   | 26  | 18.4  |
| Parity                                     | 1011+1   | 1001   | 0000             | 1001   | 1001  | 0000  |
| Week of referral                           | 18+6   | 28   | 35+2             | 32+4   | 35+4  | 26+6  |
| Serum Creatinine at referral               | 0.45   | 0.67   | 0.95             | 0.36   | 0.45  | 0.55  |
| Stone disease (active)                     | Yes  | Yes  | No               | Yes (brushite)                                     | No  | No  |
| Stone disease (previous)                   | No   | Yes  | No               | No   | No  | No  |
| Urinary tract infection at referral        | Yes  | Yes  | No               | Yes  | Yes   | No  |
| Urinary tract infection (history of)       | No   | Yes  | No               | No   | No  | No  |
| Side of dilatation                         | Right (stenting); lesser degree left side          | Left   | Right            | Left   | Right   | Right   |
| Dilatation at assessment or stenting (cm)  | 4 cm   | 3 cm   | 3.5 cm           | 3.5 cm   | 2** cm  | 6.5 cm  |
| JJ stenting (week)                         | 18 <sup>th</sup> week infection and ureteral stone | 28 <sup>th</sup> week infection and ureteral stone | No               | 20 <sup>th</sup> week infection and ureteral stone | 34 <sup>th</sup> week infection and severe pain | 27 <sup>th</sup> week infection and severe pain |
| Reason for stenting                        |  |  |                  |  |   |   |
| Maximum level of proteinuria               | 2.5 g/day  | 3.5 g/day  | 2.5 g/day        | 1.2 g/day  | 2.7 g/day                                       | 0.8 g/day                                       |
| <b>Data at delivery</b>                    |  |  |                  |  |   |   |
| Gestational age                            | 32+4   | 36 US  | 38               | 36+1   | 37+2  | 31+4  |
| Weight gain - Kg                           | 14   | 10   | 15               | 8  | 13  | 9   |
| Type of delivery                           | vaginal  | Vaginal  | vaginal          | vaginal  | vaginal   | vaginal   |
| <b>Children:</b>                           | <b>Case 1</b>                                      | <b>Case 2</b>                                      | <b>Case 3</b>    | <b>Case 4</b>                                      | <b>Case 5</b>                                   | <b>Case 6</b>                                   |
| Sex  | M  | M  | M                | F  | M   | F   |
| Weight                                     | 2400   | 2450   | 2760             | 2600   | 3110  | 2000  |
| Centile                                    | 70 <sup>th</sup>                                   | 15 <sup>th</sup>                                   | 10 <sup>th</sup> | 30 <sup>th</sup>                                   | 50 <sup>th</sup>                                | 60 <sup>th</sup>                                |
| Apgar 5'                                   | 9/9  | 9/9  | 9/9              | 9/9  | 9/9   | 8/9   |

Note: \*\*the patient was relatively de-hydrated at the first assessment; a second measurement after a few days of i.v. fluids and antibiotic therapy exceeded 3 cm. US adjusted: gestational age assessed with US datation.

kidney scars or hyperechogeneity of the kidney parenchyma); no patient had signs or history compatible with vesico-ureteral reflux. No patient had evidence of viral infection (hepatitis B, C and HIV were negative in all cases), and all had normal "basic" immunological testing (complement, antinuclear factors, ENA, ANA, immunoglobulin levels). Proteinuria typing was performed in three patients; it revealed a mixed glomerular and tubular pattern with non-selective glomerular component in all three patients.

In pregnancy, proteinuria was not limited to the phase of active infection in any patient, as it persisted or even developed (cases 4-5-6) after resolution of the acute infectious phase. Five patients underwent ureteral stenting, in 3 because of upper urinary tract infection and active stone disease, and in 2 because of severe infection and pain unresponsive to the conventional pain relievers (Table 2). Interestingly, the residual dilatation of the urinary tract was not correlated with the degree of proteinuria, which persisted even after obstruction was at least partially relieved by renal stenting (Figure 1, case 5). In no case proteinuria decreased after stenting, and in three patients it increased.

Stenting was a cause of significant morbidity in two cases: case 5 (urinary pain, urgency and frequency) and

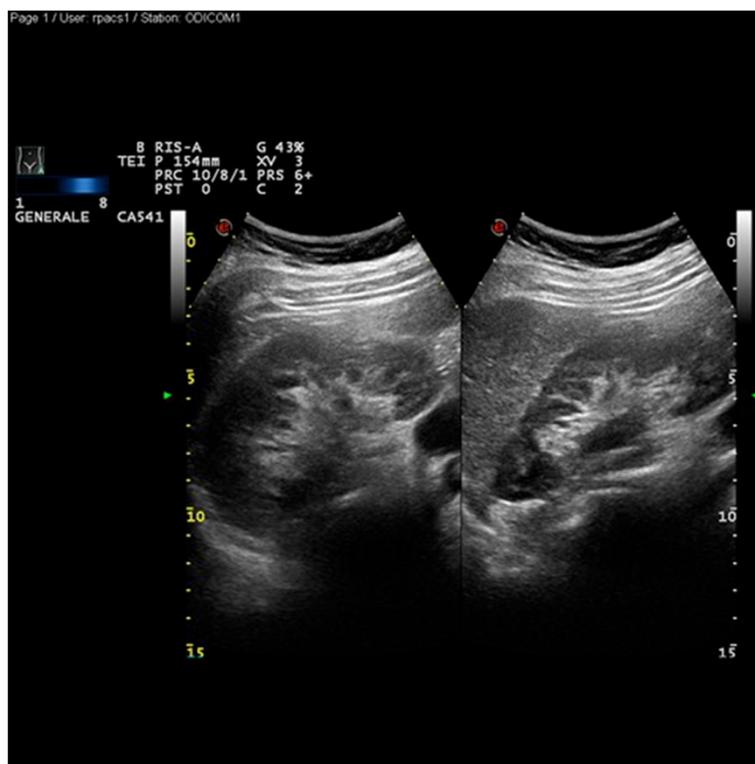
case 6, in which the invasive manoeuvre could have played a role in the preterm delivery (Table 2).

There was no evidence of an effect of the urological problem, the eventual infection or the therapies on the growth curves. In fact, the newborn was small for gestational age in only two cases, one in the subset with higher proteinuria and one in the control group with upper urinary tract infections without dilatation.

The urinary picture normalized in all patients within three months after delivery, with the disappearance of proteinuria; the ureteral stent was safely removed in all cases; it is impossible to disentangle the effect of ureteral stent removal from the effect of delivery, as the patients perform a limited number of 24 hour urine collections after delivery (usually 1 at 1 month, and - if proteinuria over 0.3 g/day is still present and decreasing - the test is repeated at 3 months).

## Discussion

The present report deals with an interesting association, not extensively studied thus far and possibly underreported, between symptomatic and/or excessive urinary tract dilatation and proteinuria in pregnancy. Indeed, our extensive Medline search revealed only one recently published case of an association between



**Figure 1** Kidney ultrasounds in case 5, after the positioning of JJ stent. Only minimal dilatation is present; however, proteinuria persisted after "JJ stenting", reducing the dilatation, and in the absence of infection. "JJ" was removed one week after delivery (proteinuria 0.5 g/day); proteinuria was absent at the control one month after delivery.

severe proteinuria, urinary tract dilatation and pregnancy in the last decade; a few other cases in which a pre-eclamptic syndrome was probably triggered by dilatation had been previously reported [13,15,20-22].

Our cases were less extensively studied than the one reported by Afzali and co-workers, also because proteinuria decreased below 0.3 g/day shortly after pregnancy in all, thus limiting the diagnostic potential which is higher after delivery [13]. Interestingly, in both our small series and the recently reported case, renal function was normal and no history of kidney disease (with particular reference to reflux nephropathy) was available nor was a different cause of kidney disease suggested by the ultrasound patterns. This differentiates our cases from reports of the risks of pregnancy in women with vesicoureteral reflux in infancy, a potential risk factor even in the presence of normal kidney function [20-23].

It is well known that proteinuria may develop late in urological disease. This is usually considered to be caused by nephron loss and a poor prognostic sign, occurring in late stages of the disease when significant reduction of the kidney parenchyma is usually evident at ultrasounds [19,24,25]. However, neither our patients nor the case reported by Afzali displayed such a picture and the kidney function was normal in all cases. A “renal reflex” has been postulated in experimental animals and in humans, and was called into question in the case report by Afzali and co-workers [13,26,27].

It is very difficult to suggest a univocal interpretation of the observed data.

First of all, our cases were symptomatic or displayed excessive dilatation (over 3 cm); this referral pattern differentiates our observations from those of other studies, in which mild or minimal dilatations are reported, in the assessment of the frequency of urinary tract dilatation in pregnancy [24,25]. Thus, our series may be considered as negatively selected, as small symptomless dilatations are neither identified nor referred (the use of maternal kidney ultrasounds in pregnancy is very limited in the clinical practice). Furthermore, in the presence of proteinuria, ultrasounds are not routinely performed in all settings, and a relationship between the so-called pregnancy-induced proteinuria and non symptomatic urinary tract dilatation may escape diagnosis.

Therefore, we will limit our report to the description of an association that might be more frequent than previously reported, possibly because of a trigger effect of pregnancy on the development of proteinuria in the context of various kidney diseases, including symptomatic or severe urinary tract dilatation. As urinary picture normalized in all patients after delivery and ureteral stent removal; it was impossible to disentangle the effect of each ones. However, the clinical relevance in the differential diagnosis with pre-eclampsia is unaffected by the cause of proteinuria.

A role for the increase in abdominal pressure may be postulated, together with a facilitating role of the urinary tract infections, where present. However, possibly to the negative selection of the cases, mentioned above, a clear-cut relationship was not identified.

Pregnancy may facilitate the development of proteinuria in the context of severe-symptomatic urinary tract dilatation via the changes in the metabolic milieu, through hyperfiltration or both, thus suggesting to further investigate in these fields. One possible explanation is that proteinuria increases steadily in pregnant women as the levels of the soluble fms-like tyrosine kinase-1 (sFlt-1) rise, whose effect on podocytes is to increase proteinuria. Patients with chronic interstitial nephritis might have reached the tubular maximum of reabsorption and display proteinuria near term, when circulating sFlt-1 is at its highest [28,29].

The striking association with ureteral stenting in our series needs further confirmation on a larger scale; indeed, there is a strong selection bias, as only the most symptomatic cases usually undergo invasive procedures. A role of iatrogenic vesicoureteral reflux (linked to the presence of a ureteral stent) in the persistence of tubular damage (and/or of the inflammatory changes associated with urinary reflux and infection) can be postulated, but once again this awaits further confirmation in a prospective larger-scale analysis.

Our study has several limitations, partly shared by other observational studies in pregnancy: the problem of low grade proteinuria is very important in particular in a situation in which the upper physiological limits “touch” the limit for the definition of a severe disease (pre-eclampsia). Hence, we may have missed some cases with low-grade proteinuria and urinary tract dilatation, who tested negative at conventional urinalysis; conversely, the cases who tested positive at urinalysis or who were diagnosed with proteinuria at 24 hour urine collections were repeatedly controlled, thus ensuring against false positives (Tables 1, 2).

The interest in our report is mainly clinical, since it raises the hypothesis of an alternative source of proteinuria in a context in which pre-eclampsia is the most likely diagnosis. The clinical management would be different, for example the controversial “fluid management” often employed to offset the pre-eclamptic response may even be harmful in the context of urinary tract dilatation.

The treatment of the pregnant patient presenting with upper urinary pain and fever, or a kidney stone is quite obvious, but the differential diagnosis may be difficult in the absence of these symptoms. Hence, our case series suggests that an obstructive origin should be considered in the differential diagnosis of proteinuria in pregnancy, particularly in cases presenting without hypertension and with normal renal function. Further research in this

field, with coordinated nephro-urological and gynaecological teams, is recommended.

## Conclusions

This report suggests considering urinary tract dilatation in the differential diagnosis of the new onset of proteinuria in pregnancy and, vice versa, systematically testing for proteinuria in pregnant patients with severe and symptomatic urinary tract dilatation. Our series also suggests a possible association between “JJ stenting” and the development of proteinuria, even though the association may be due to the negative selection of cases needing urological interventions.

This diagnosis could be very important in the differential diagnosis with other pregnancy-related conditions, such as pre-eclampsia. Greater awareness of this issue may help clarify the mechanisms underlying the development of proteinuria in the context of obstructive kidney diseases.

## Competing interests

The authors declare that they have no competing interests.

## Authors' contributions

GBP, AV and TT designed the study; GBP and RA drafted the manuscript. FNV, GD and MCD participated to the management of the patients and performed the collection of the data of the patients in the Nephrology setting. SP took care of data collection and of the statistical analysis, supported by GD. ADP and AV carried out the ultrasound analysis. FP followed patients in the Urologic aspects. All authors read and approved the final manuscript.

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