Pediatr Nephrol (2006) 21: 510–516
DOI 10.1007/s00467-006-0011-z

ORIGINAL ARTICLE

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Gender and vesico-ureteral reflux: a multivariate analysis

Received: 15 August 2005 / Revised: 25 September 2005 / Accepted: 27 September 2005 / Published online: 14 March 2006

Abstract The aim of this retrospective cohort study was to describe the characteristics of patients with primary vesico-ureteral reflux (VUR) with special attention to gender-specific differences. Between 1970 and 2004, 735 patients were diagnosed with VUR and were systematically followed in a single tertiary renal unit. The following variables were analyzed: race, age at diagnosis, clinical presentation, weight and height Z-score, unilateral/bilateral reflux, VUR grade, renal damage, severity of renal damage, constipation, and dysfunctional voiding. Comparison of proportion between genders was assessed by the chi-square test with Yates' correction. The logistic regression model was applied to identify independent variables associated with gender. A survival analysis was performed to evaluate VUR resolution. After adjustment, five variables remained independently associated with male gender at baseline: non-white race [Odds ratio (OR) = 1.98, 95% confidence interval (95% CI) 1.33–2.95, P=0.001], moderate/severe grade of reflux (OR=2.16, 95% CI 1.45–3.22, P<0.001), severe renal damage (OR=1.60, 95% CI 1.04–2.52, P=0.04), age at diagnosis <24 months (OR=1.79, 95% CI 1.23–2.60, P=0.002), and antenatal clinical presentation (OR=3.56, 95% CI 1.91–6.63, P<0.001). Follow-up data were available for 684 patients (93%). Median follow-up time was 69 months (range 6 months to 411 months). Girls had a greater risk of urinary tract infection (UTI) during follow-up than boys (OR=1.68, 95% CI 1.18–2.38, P=0.003). There was no difference in progression to chronic renal insufficiency (CRI) between boys (3.8%) and girls (2.4%) during this period of follow-up (OR=1.58, 95% CI 0.59–4.15, P=0.44). Gender as an isolated variable is a poor predictor of clinical outcome in an unselected series of primary reflux. Although boys had a more severe pattern at baseline, girls had a greater risk of dysfunctional voiding and recurrent UTI during follow-up.

Keywords Vesico-ureteral reflux · Gender · Reflux nephropathy · Urinary tract infection · Voiding dysfunction

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Introduction

The well-known combination of primary vesico-ureteral reflux (VUR) and urinary tract infection (UTI), predisposing to pyelonephritis, renal scarring, hypertension, and chronic renal disease, has been the basis for diagnostic and therapeutic procedures in the past 25 years [1]. A number of series of prenatally detected VUR has added new perspectives to this setting, suggesting that there are two distinct patterns of VUR [2–5]. First, a group of infants, predominantly girls, with mild reflux and normal kidneys, and another group with severe reflux associated with kidney damage, almost exclusively a male disorder.

The recognition of VUR as a heterogeneous disease is the first step towards a tailored diagnostic and therapeutic approach. The clinical implication of identification of two main clinical pictures of VUR is that these groups probably have to be managed differently. Although previous studies of VUR detected in the investigation of UTI have already reported a preponderance of boys with severe reflux and generalized renal damage, this issue has not been explored in a specific study with adjustment for possible confounders [6–8].

In the present retrospective cohort study, we analyzed the clinical features and outcomes of 735 children and adolescents with primary VUR, with the purpose of

investigating gender-specific differences in a multivariate analysis.

Materials and methods

The study group comprised 735 patients diagnosed with primary VUR who were followed at the Pediatric Nephrourology Unit of the University Hospital (UFMG, Belo Horizonte, Brazil) between 1970 and 2004. VUR associated with posterior urethral valves, ectopic ureterocele, neurogenic bladder, and other obstructive uropathies was excluded from the analysis. At entry, the diagnosis of VUR was made by conventional voiding cysto-urethrography (VCUG). Four patients were excluded from analysis because their initial examination was a direct isotope cystogram. Reflux grade was classified on first VCUG according to the system proposed by the International Reflux Study Committee [9]. All children were maintained on antibiotic prophylaxis consisting of 1–2 mg/kg trimethoprim or 1–2 mg/kg nitrofurantoin as a single daily dose. After the initial investigation patients were followed according to a systematic protocol described in detail in a preliminary report on our series [10]. Briefly, the clinical approach consisted of full physical examination, including evaluation of growth and blood pressure, performed at 6-month intervals. Urine cultures were obtained during follow-up visits or during any febrile episodes. Recurrent UTI was defined as growth of at least 100,000 cfu/ml in urine obtained by bag or a mid-stream sample, with fever (38.0°C or more) or urinary symptoms. Plasma creatinine was determined at baseline and yearly thereafter. Glomerular filtration rate was estimated by the method of Schwartz et al. [11]. Chronic renal failure (CRF) was defined as a glomerular filtration rate <75 ml/min per 1.73 m^2 body surface area in two consecutive examinations. Blood pressure measurements were performed with a standard sphygmomanometer using a cuff of appropriate size as recommended by the Working Group of the National High Blood Pressure Education Program [12]. Reference values and definitions of normal blood pressure were based on the Second Task Force Report [13].

Baseline and follow-up imaging consisted of conventional VCUG or a direct isotope cystogram at 2-year intervals during the first 48 months after diagnosis and at 3-year intervals thereafter. A DMSA scan and ultrasonography were performed at approximately the same intervals. For statistical analysis, VUR was classified as mild (grades I–II) and moderate/severe (grades III–V). For analysis, patients with bilateral reflux were categorized by the higher grade of reflux. Renal damage was ascertained at admission by ^{99m}Tc-DMSA in 553 patients (75.2%). Renal scarring in patients enrolled up to the mid-1980s was evaluated by excretory urography in 89 children (12.1%) or by ultrasonography in 93 patients (12.6%) because a DMSA scan was unavailable at that time in our Unit. Renal damage classification was qualitative according to the findings obtained in imaging studies and defined as normal (no alterations), mild (localized damage), moderate (two or more scars), or severe (contracted unit).

The following variables were analyzed: race, age at diagnosis (cut-off point 24 months), clinical presentation (antenatal hydronephrosis/UTI), weight and height Z-score; unilateral/bilateral reflux, VUR grade (I–II/III–V), renal damage (absence/presence), constipation (absence/presence), and dysfunctional voiding (absence/presence). Dysfunctional voiding was investigated in 671 patients (91.2%) and constipation in 660 (89.8%). Dysfunctional voiding was defined by the presence of daytime incontinence, symptoms of urgency and frequency associated with sonography parameters including residual urine (greater than 20% of bladder capacity) and large bladder capacity (greater than twice the expected normal value for age) [14]. Presence of dysfunctional voiding in patients enrolled up to 1990 was defined only by clinical history, because comprehensive sonography was not available. When dysfunctional elimination syndrome was identified, specific treatment was instituted, including regular fluid intake, anticholinergic medication, behavioral modification program, and a combination of dietary manipulation, stool softeners, and laxatives for constipation.

The analysis was conducted in two steps. In the first step, a univariate analysis was performed by the chi-square test with Yates' correction for comparison of proportions between boys and girls at baseline. For patients with bilateral reflux, only the unit with the higher grade of reflux was considered for analysis. A logistic regression model was applied to identify variables that were independently associated with gender. Only those variables that were found to present different proportions between genders (P<0.25) were included in the regression model. Then, using a backward elimination strategy, we included in the final model those variables that retained a significant independent association (P<0.05). Survival analysis was performed by the Kaplan–Meier method in order to evaluate reflux resolution [15]. Differences between genders were assessed by the two-sided log-rank test. Odds ratio (OR) and 95% confidence intervals (95% CIs) were used for comparison of risk between genders. The Mann–Whitney test was used for comparison of continuous variables such as age at diagnosis, differential DMSA uptake, and renal function based on serum creatinine.

Results

Baseline data

A total of 735 patients was included in the analysis. Two hundred and eight were male (28.3%) and 527 were female (71.7%). There were 582 (79.2%) white patients and 153 non-white patients (20.8%). Twenty-three patients (3.1%) were admitted between 1970 and 1980, 141 (19.2%) between 1980 and 1990, and 571 (77.7%) after 1990. The mean age at diagnosis of reflux was 2.3 years (SD 1.6). Reflux was detected before 2 years of age in 439 children (59.7%). The clinical presentation was urinary tract infection in 681 children (92.6%), fetal hydronephrosis in 52 (7%), and familial screening in only two patients. VUR

Table 1 Univariate analysis of baseline characteristics according to gender

Characteristic	Boys (*n*=208)	Girls (*n*=527)	X^2	*P*
Clinical features				
Race				
Non-white	57	96		
White	151	431	7.63	0.004
Age at diagnosis				
<24 months	144	295		
>24 months	64	232	10.9	0.001
Presentation				
Fetal	41	11		
UTI	166	515	70.7	<0.00
Weight Z score				
<−2.0	24	54		
>−2.0	183	472	0.27	0.34
Height Z score				
<−2.0	23	40		
>−2.0	178	479	2.5	0.07
Dysfunctional voiding				
Present	23	40		
Absent	161	396	2.5	0.07
Constipation				
Present	21	79		
Absent	163	397	2.71	0.06
Reflux features				
Laterality				
Unilateral	97	257		
Bilateral	111	270	0.27	0.33
Grade				
Mild (I/II)	45	210		
Moderate/severe (III–V)	163	317	21.8	<0.00
Method of determination of renal damage				
DMSA scan	160	393		
Urography	27	62	1.80	0.40
Ultrasonography	21	72		
Renal damage				
Present	100	210		
Absent	108	317	3.81	0.05
Severe renal damage				
Present	43	69		
Absent	165	458	6.06	0.013

was bilateral in 381 (51.8%) patients, for a total of 1,116 renal units. Renal damage was detected at admission in 319 patients (43.4%) and in 385 renal units (34.5%). The main clinical and radiological characteristics and unadjusted univariate analysis are shown in Table 1. Six variables presented a significantly different distribution between genders: race, age at diagnosis, clinical presentation, renal damage, and severe renal damage. Non-white ethnicity was more frequent in male (27.4%) than in female (18.2%) patients. One hundred and four male patients (69.2%) had a diagnosis of VUR before 2 years of age, whereas 55.9% (295/527) girls had a diagnosis of VUR before 24 months of age. The median age at diagnosis was 11 months (range 1 month to 14 years) for boys and 20.9 months (range 1–14 years) (P<0.001) for girls. Boys had more frequent (19.7%) prenatal identification of VUR than girls (2%). Severe reflux (III–V) was more frequent in boys (78.3%) than in girls (60%). Renal damage at admission was more frequent in boys (48%) than in girls (39.8%). Severe renal damage was also more frequently seen in boys (20.6%) than in girls (13.0%). In 253 patients with unilateral reflux who underwent a DMSA scan at admission, differential uptake was significantly smaller in boys than in girls. The median was 38.5% (range 6% to 90%) for 68 boys, as opposed to 46.2% (range 5% to 70%) for 179 girls (P=0.003). Dysfunctional voiding was identified in 94 (19.1%) girls but in only 20 boys (11%). Constipation was also more frequently detected in female (16.5%) than in male (11.4%) patients. In multivariate analysis, five variables remained independently associated with male patients: non-white, age at diagnosis <24 months, fetal presentation, grade of VUR, and severe renal damage (Table 2). The multivariate analysis was also performed excluding patients with prenatally detected VUR. Even after exclusion of these patients, age at diagnosis <24 months of age remained as a variable associated with boys (Table 3).

Follow-up data

Follow-up data were available for 684 patients (93%). One hundred and ninety four were boys (28.4%) and 490 were girls (71.6%). Sixteen boys (7.7%) and 37 girls (7%) were lost to follow-up. Median follow-up time was 69 months (range 6 months to 411 months). A total of 382 (55.8%) patients were followed up for more than 5 years and 138 (20%) for more than 10 years. The median follow-up time for boys and girls was 65.2 months (range 6–412 months)

Table 2 Factors associated with male patients with primary VUR after adjustment by regression logistic model (*n*=735)

Factor	Coefficient	OR	95% CI	*P*
Race (non-white)	0.685	1.98	1.33–2.95	0.001
VUR grade (III–V)	0.773	2.16	1.45–3.22	<0.001
Severe renal damage (presence)	0.473	1.60	1.04–2.52	0.04
Age at diagnosis (<24 months)	0.585	1.79	1.23–2.60	0.002
Presentation (fetal)	1.271	3.56	1.91–6.63	<0.001

Table 3 Factors associated with male patients with primary VUR identified by UTI after adjustment by regression logistic model (n=683)

Factor	Coefficient	OR	95% CI	P
Race (non-white)	0.700	2.01	1.32–3.05	0.001
VUR grade (III–V)	0.717	2.04	1.35–3.09	0.001
Severe renal damage (presence)	0.518	1.68	1.05–2.70	0.03
Age at diagnosis (<24 months)	0.457	1.58	1.09–2.30	0.017

and 71.6 months (range 9–290 months), respectively. There was no difference in median follow-up time between genders (P=0.17).

Of 684 patients, 60 (8.8%) were submitted to surgery (ureteral re-implantation in 44, nephrectomy in ten, and urinary diversion in six) and 624 (91.2%) were conservatively managed. The type of surgery according to gender was as follows: ureteral re-implantation (19 boys and 25 girls), nephrectomy (5/5), and urinary diversion (4/2). Of 22 patients admitted between 1969 and 1979, 12 (54.5%) were submitted to surgery, whereas this proportion was 13.8% (19/137) for children admitted between 1980 and 1989 and 5.5% (29/525) for those admitted after 1999 (χ^2=68.9, P<0.001). Boys were operated upon more frequently than girls. Of 194 boys, 28 (14.4%) were submitted to surgery, as opposed to only 32 (7%) of 458 girls (χ^2=10.8, P=0.001).

Urinary tract infection occurred in 394 (57.6%) of 684 children during follow-up. As a whole, 519 (75.8%) patients presented less than three episodes of urinary infection during follow-up (including 290 patients who did not present any UTI). Patients admitted until 1989 had a greater risk of UTI than children enrolled between 1990 and 2004 (OR=1.77, 95% CI 1.20–2.62, P=0.003). This difference was independent of the time of follow-up (OR=1.56, 95% CI 1.06–2.3, P<0.025). There was no difference in occurrence of UTI between children operated upon (61%) and those conservatively managed (57%) (χ^2=0.44, P<0.30). Girls had a greater risk of UTI during follow-up than boys (OR=1.68, 95% CI 1.18–2.38, P=0.003).

During follow-up, 505 (80%) of 624 patients conservatively managed were submitted to serial VCUG. Of 505 patients examined, 250 (50%) showed resolution. There was no significant difference between genders in reflux resolution (Fig. 1).

Of 684 patients, 587 (85.8%) underwent renal imaging in order to re-evaluate renal damage near the end of follow-up. The most frequent renal imaging was a DMSA scan in 385 patients, followed by renal ultrasonography in 184, and excretory urography in only 18 children. There was no significant difference in renal imaging between genders (χ^2=1.1, P=0.57). At the end of follow-up there was no significant difference in presence of renal damage between genders. Renal damage was diagnosed in 86 of 162 boys (53%) and in 191 of 425 girls (44.9%) (χ^2=2.80, P=0.09). On the other hand, severe renal damage was more prevalent in boys (26.5%) than in girls (15%) (χ^2=9.62, P=0.001). Development of new scars was analyzed in 352 children submitted to at least two DMSA scans. New renal scars were detected in 18 patients (ten with bilateral reflux). The distribution of the grade of reflux in these patients was as follows: II (27.8%), III (38.8%), IV (27.8%), and V (5.6%). Fourteen (77.7%) of these 18 children presented recurrent UTI. Nine (50%) patients presented voiding dysfunction. The number of episodes of UTI ranged from two to five

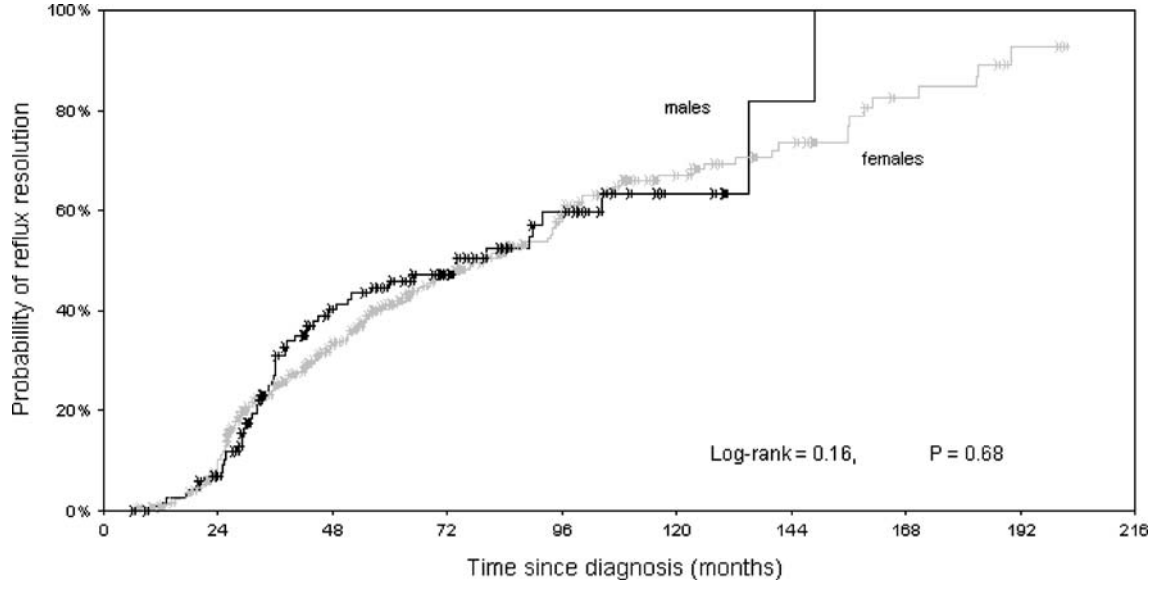

Fig. 1 Kaplan-Meier survival curves showing the probability of reflux resolution according to gender

episodes. All new scars were classified as mild localized damage. Girls had a greater risk of occurrence of new renal scars, although the difference was not statistically significant. Fourteen of 252 girls (5.5%) and four of 100 boys (4%) presented new renal scars (OR=1.42, 95% CI 0.42–5.22, *P*=0.74). Differential DMSA uptake was smaller in boys than in girls for 164 patients with unilateral reflux submitted to a DMSA scan at the end of follow-up. The median was 36% (range 5% to 56%) for 37 boys, as opposed to 46% (range 10% to 64%) for 127 girls (*P*=0.03).

At the end of follow-up, 21 (2.8%) patients had developed chronic renal insufficiency (seven of them end-stage renal disease). Boys had a greater risk of progression to CRF than girls, although the difference was not statistically significant (OR=1.58, 95% CI 0.59–4.15, *P*=0.44). Of 21 patients with CRI, three presented a contralateral hypoplastic kidney and two contralateral renal agenesis. Sixteen patients presented bilateral severe reflux with renal damage. Of 684 patients followed, 76 (11.1%) presented bilateral severe reflux or unilateral severe reflux with contralateral anomaly. In this subgroup, eight (22.8%) of 35 boys and 13 (31.7%) of 41 girls developed CRF. Twenty patients (2.7%) presented hypertension. There was also no difference in the development of hypertension between boys (4.6%) and girls (2.2%) (OR=2.12, 95% CI 0.79–5.61, *P*=0.15). At the end of follow-up, serum renal function was available for 595 (87%) of 684 patients. There was no difference in serum renal function between genders, including those children with CRF. Serum urea ranged from 10 mg/dl to 186 mg/dl in boys (median 27 mg/dl) and from 10 mg/dl to 291 mg/dl in girls (median 25 mg/dl) (*P*=0.06). Serum creatinine ranged from 0.25 mg/dl to 10 mg/dl in boys (median 0.60 mg/dl) and from 0.20 mg/dl to 14.0 mg/dl in girls (median 0.60 mg/dl) (*P*=0.86). The estimated median glomerular filtration rate was 119 ml/min per 1.73 m^2 (range 8 ml/min per 1.73 m^2 to 226 ml/min per 1.73 m^2) for boys and 127 ml/min per 1.73 m^2 for girls (range 7 ml/min per 1.73 m^2 to 258 ml/min per 1.73 m^2) (*P*=0.14).

A total of 138 patients (40 males) was followed for more than 10 years. Serum renal function was available for 126 (91.3%) patients. There was no difference in serum renal function between genders. Serum creatinine ranged from 0.4 mg/dl to 10 mg/dl in boys (median 0.80 mg/dl) and from 0.30 mg/dl to 14.0 mg/dl in girls (median 0.70 mg/dl) (*P*=0.23). The estimated median glomerular filtration rate was 120.5 ml/min per 1.73 m^2 (range 11 ml/min per 1.73 m^2 to 192 ml/min per 1.73 m^2) for boys and 125.5 ml/min per 1.73 m^2 for girls (range 7 to 223) (*P*=0.79).

Discussion

In this retrospective cohort study we explored possible differences between genders in an unselected pediatric population with primary VUR. Our findings confirmed that, at baseline, boys presented more severe reflux with a greater prevalence of generalized renal damage. However, in our series, this difference apparently did not influence the clinical outcome. We are aware of several limitations associated with the retrospective design of our study. The possible main weakness is the limited control over the measurements of variables included in the analysis. For example, the importance of dysfunctional voiding in the clinical course of VUR was fully recognized only after the 1990s. Thus, this information for patients enrolled in the 1980s was ascertained by clinical history and might have been underestimated in these children. Because of the great span of time there were inevitable inconsistencies in the approach to the patients through the decades. Nevertheless, some features of the study may increase the strength of our findings, such as the size of our sample, management by the same medical team, and length of follow-up period.

Previous cohort studies of primary VUR before the antenatal diagnosis era had already shown a preponderance of boys with severe reflux and generalized renal damage [6, 7]. In a cohort study of children with UTI and VUR, Goldraich and Goldraich [8] reported that the diagnosis of reflux was made significantly earlier in boys and that boys presented a greater prevalence of severe renal damage independent of grade of reflux. In a review article, Risdon [16] called attention to pathogenic factors involved in reflux nephropathy and suggested that at least two main mechanisms operate: acquired segmental scarring due to intrarenal reflux and congenital maldevelopment (renal dysplasia). Data from series of VUR detected in investigation of fetal hydronephrosis have supported this evidence [17–20]. In the larger published series, Yeung et al. [5] have shown a significantly greater prevalence of abnormal kidneys in boys (40%) than in girls (12%). Generalized kidney damage affected 5% of girls' units compared with 28% of boys' units. Most of the severely affected kidneys had no exposure to UTI (85%). In a multicenter retrospective study in Japan, Nakai et al. [21] demonstrated in a cohort of infants with primary VUR a 42% prevalence of diffuse parenchymal lesion in boys, whereas in girls it was 25%. On the other hand, the prevalence of focal parenchymal lesion was almost similar in boys (30%) and girls (27%). In our unselected pediatric population, after adjustment by covariates there was an association between boys and moderate/severe reflux and severe renal damage. In addition, VUR was detected earlier in boys, and boys were diagnosed more frequently by investigation of fetal pelvic dilatation. Of note, in our analysis after adjustment by logistic regression, both higher grades of reflux and severe renal damage remained associated with boys in the multivariate model. These findings suggest that, although severe reflux and renal damage are highly associated, the presence of a greater proportion of shrunken kidneys in boys is independent of the grade of reflux. Taken together, these data show that prenatal diagnosis of sterile reflux has called attention to a fact that was seldom considered previously, i.e., that primary VUR is a heterogeneous disease, unlikely to be a single nosological entity, and should be regarded as a marker for generalized disease of the whole urinary tract. This includes being born with renal

dysplasia, altered urinary bladder contractility or function, and a predisposition to urine infection which is not cured when VUR regresses or is surgically corrected [1].

In the medium to long-term follow-up the clinical outcome of primary VUR was relatively benign in our series. As a whole, the prevalence of CRF was 2.8%, and the prevalence of hypertension was 2.7%. The decline of renal function occurred in those patients with severe bilateral renal damage or in those children with contralateral renal dysplasia/hypoplasia. These conditions were congenitally determined, and, probably, the management of primary VUR could scarcely contribute to improving the prognosis of these patients. Our prevalence of CRF might have been slightly underestimated because of the medium-term time of follow-up. In the study by Smellie et al. [22], with a longer follow-up (10–41 years), over 90% of a cohort of 226 adults who had primary VUR were clinically well and normotensive, although 38% had renal scarring and 30% had severe reflux at admission. In our study, there was no significant difference between boys and girls in the occurrence of hypertension and decline of renal function, although a greater proportion of boys presented an adverse outcome. Similarly, Smellie et al. [22] have shown a prevalence of 2.6% (6/226) of abnormal plasma creatinine levels in 226 patients. In their series, two (5.4%) of 37 male patients and four (2.1%) of 189 female patients had already presented raised plasma creatinine levels during childhood. The renal function of 162 of these patients was evaluated in adult life, and nine presented abnormal plasma creatinine levels (three men and six women). These findings confirm CRF as a rare complication of primary VUR. On the other hand, probably because of its high incidence, VUR has been identified as the principal cause of CRF in children. It is noteworthy that data from a population-based multicenter registry of children with CRF born after 1975 (ItalKid registry) have demonstrated a striking prevalence of male subjects with VUR as the main cause of renal failure [23]. Of 1,197 patients enrolled, 284 (25.7%) were affected by primary reflux and 220 (77.5%) of them were male. In addition, this registry has also shown a combination of earlier diagnosis and severe reflux in boys. We agree with the authors that the remarkable underrepresentation of girls in the ItalKid registry can be attributed in part to the more widespread and aggressive treatment of VUR and UTIs over the past 30 years. Thus, probably new registries such as ItalKid better reflect the current morbidity of primary reflux. Also, it cannot be excluded that the subgroup of boys with congenital renal damage accounts for the apparent absence of an effect of management of VUR over the past 30 years on the incidence of end-stage renal disease (ESRD) attributable to reflux nephropathy [24]. Taken together, these data suggest that boys have a greater risk of renal failure than girls. Probably, the absence of statistical significance in the comparison of risk of CRF in our series was due to the small number of patients with impairment of renal function. However, in registries of CRF in which data from many centers were pooled together, such as the ItalKid project, this difference in risk became evident.

In spite of the use of prophylactic antibiotics or of a surgical approach, 57.6% of the children had breakthrough UTIs during follow-up and girls had a greater risk of UTI than boys. As expected, dysfunctional voiding and constipation were also found more frequently in girls. These clinical features may account, in part, for the preponderance of urinary infections in girls [25, 26]. Goldraich and Goldraich [8] reported an incidence of breakthrough UTIs in 87 (43%) of 202 children managed conservatively and followed for a mean time of 68.7 months. Breakthrough UTI was significantly more common in girls (47%) than in boys (28%). In the International Reflux Study in Children, UTI developed during the first 5-year follow-up period in 59 patients (38%) in the medical group and in 59 (39%) in the surgical group, but the incidence of pyelonephritis was higher in the medical group (21%) than in the surgical group (10%) [27]. Sjostrom et al. [28] reported on a cohort of infants with severe reflux and showed that half the children had breakthrough UTIs during follow-up. Interestingly, they found a strong correlation between recurrent infections, bladder dysfunction, and no resolution of the reflux. Therefore, a probable explanation for the high incidence of recurrent urinary infections in our series is a combination of many factors. Interestingly, patients admitted until the end of the 1980 decade had a greater risk of UTI than children with a diagnosis of VUR after 1990. Possibly, this fact reflects an improvement in our understanding of the risk factors for UTI in this population, especially the recognition and treatment of voiding dysfunction and constipation. However, it is important to point out that the issue of compliance with medical treatment has been scarcely studied and may account for occasional failure of long-term prophylactic antibiotic programs [29].

The possible main clinical implication of our study is that, as an isolated variable, gender is a poor predictor of clinical outcome in an unselected series of primary VUR. Although boys had a more severe pattern at baseline, girls had a greater risk of recurrent UTI and dysfunctional voiding during follow-up. Consequently, new strategies for the management of VUR will require the development of predictive risk models of adverse outcome, including several variables such as gender, age at diagnosis, severity of reflux, severity of renal damage, laterality, dysfunctional voiding, and associated renal and urological abnormalities.

Acknowledgments This study was partially supported by CNPq (Brazilian National Research Council), Pró-Reitoria de Pesquisa (UFMG), and FAPEMIG. R.M.V. and M.A.V. were recipients of CNPq fellowships.

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