Pediatr Nephrol (1999) 13:859–864

ORIGINAL ARTICLE

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Prognostic factors in fetal hydronephrosis: a multivariate analysis

Received: 24 August 1998 / Revised: 7 December 1998 / Accepted: 11 December 1998

Abstract With the increasing use of obstetric echography fetal hydronephrosis has been reported more frequently. The purpose of this study was to identify prognostic factors associated with adverse outcome, such as renal failure and death, in fetal hydronephrosis. One hundred and forty-eight children with fetal hydronephrosis were admitted, submitted to a systematic protocol, and prospectively followed. Prognostic factors associated with fetal echography and clinical and laboratory findings on admission were studied. The median follow-up was 39 months. The analysis was conducted in two steps. In a univariate analysis, variables associated with adverse outcome were identified by the Kaplan-Meier method. The variables that were significantly associated with adverse outcome were then included in a multivariate analysis. This analysis, using the multivariate Cox's model, was performed to identify variables that were independently associated with a worse prognosis. Only variables that remained independently associated with adverse outcome were included in the final model. After final adjustment by Cox's multivariate model, three variables were identified as independent predictors of adverse outcome: oligohydramnios, prematurity, and glomerular filtration rate lower than 20 ml/min. Thus, in the presence of oligohydramnios, prematurity, and abnormal renal function, the medical team must plan appropriate follow-up for infants at health centers prepared to investigate and treat uropathies in newborns.

Key words Fetal · Hydronephrosis · Ultrasonography · Oligohydramnios · Prognosis · Multivariate analysis

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Introduction

Hydronephrosis is the most-common congenital condition detected by prenatal ultrasonography [1]. Some studies have shown that the frequency of hydronephrosis is 1 in 500–700 deliveries [2, 3]. Prospective studies have calculated that the incidence of detectable urinary dilatation in utero ranges from 0.48% to 1.4% [4, 5]. Prenatal ultrasonography frequently reveals isolated hydronephrosis, either bilateral or unilateral. However, hydronephrosis can be associated with ureteral, bladder, and amniotic fluid abnormalities.

Prenatal detection of urinary tract anomalies provides the opportunity to influence favorably the pregnancy and postnatal approach. The physician should explain to the family the possible implications of the prenatal ultrasound findings and propose the best approach to management. The medical team must have knowledge of the prognostic significance of findings associated with prenatally detected hydronephrosis [6]. Therefore, accurate prediction of infants with a poor outcome is highly desirable. However, the factors that independently predict an adverse outcome in fetal hydronephrosis have not been established. Previous studies have proposed oligohydramnios as an important predictor of a poor prognosis [7, 8]. Other prognostic factors, such as detection at 24 weeks of gestation or earlier and the degree of hydronephrosis, have been reported in neonates with prenatally detected posterior urethral valves [9, 10].

In this study, we analyzed the outcome of 148 children with prenatally detected hydronephrosis. The purpose was to identify variables that are independent predictors of death and chronic renal failure by using data

available at the time of patient admission, before the definite diagnosis of the uropathy.

Patients and methods

Patients

One hundred and fifty-four babies born at Hospital das Clínicas-UFMG (Belo Horizonte, Brazil) between January 1985 and July 1995 who were found to have hydronephrosis by prenatal ultrasonography were referred to our unit. Of these, 121 were seen after 1990. Among the 154 cases, 6 were lost to follow-up and could not be included in the analysis. Fetal anatomy was carefully investigated by the staff obstetricians. Hydronephrosis was defined, qualitatively, as dilatation of the pelvi-caliceal system [11]. Dilatation was considered to be present if the maximum anterior-posterior diameter of the fetal renal pelvis was equal or greater than 5 mm. Specific ultrasound findings, such as the presence of renal, ureteral, and bladder involvement, the volume of amniotic fluid, and gestational age were recorded. Postnatally, neonates were investigated according to a systematic protocol illustrated in Fig. 1. All were placed on prophylactic antibiotics at birth and prophylaxis was continued in children with urinary tract obstruction until corrective surgery was performed, and in newborns with ureteral reflux until reflux resolved.

On admission, serum renal function (creatinine and urea), urinalysis, and urine culture were performed. Glomerular filtration rate was estimated by the method of Schwartz et al. [12]. If neonates were admitted during the 1st week of life, the serum renal function tests were postponed until at least 3 days of life. Perinatal data (birth weight, birth stature, Apgar scores) were also recorded. Palpation by the unimanual abdominal technique was performed in all newborns during the first 3 days of life [13].

Prognostic factors

The prognostic indices used are based on patient data at the time of entry into the study, before the definitive diagnosis of the uropathy. Variables were divided into three groups: (1) prenatal ultrasonography, (2) initial clinical findings, and (3) initial laboratory findings. The following data were also recorded: (1) gestational age at diagnosis (weeks of gestation); presence of megaureter, megacystis, cysts, oligohydramnios, and bilateral findings; (2) birth weight, prematurity, Apgar scores, systolic pressure, abnormal palpable kidneys; (3) serum creatinine, serum urea, glomerular filtration rate, presence of bacteriuria (more than 100,000 colony-forming units/ml), hematuria (more than 5 red blood cells/mm^3), proteinuria (qualitative by the dipstick method), and pyuria (more than 10 white blood cells/mm^3). Only results of the first laboratory tests and physical examination were recorded. The variables studied are shown in Table 1. The code used for dichotomous variables was 1 (presence) or 0 (absence). Continuous variables were dichotomized using either the traditional cut-off level (birth weight, Apgar scores, systolic pressure) or maximum likelihood estimation.

Adverse outcome

Adverse outcome was defined as death or chronic renal failure during follow-up. Chronic renal failure was defined as a glomerular filtration rate lower than 80% of normal level [14].

Statistical analysis

The analysis was conducted in two steps. In the first step, a univariate analysis was performed to identify variables that were significantly associated with adverse outcome. Univariate analyses were performed by the Kaplan-Meier method [15, 16]. Differences between patient subgroups were assessed by the two-sided log rank test. Continuous variables were dichotomized by maximum likelihood estimation. In this analysis, the higher value corresponds to the cut-off point that best differentiates patients with an adverse outcome from patients with a favorable outcome.

Cox's regression model was applied to identify variables that were independently associated with adverse outcome [17]. Only those variables that were found to be associated with adverse outcome by univariate analysis ($P<0.2$) were included in Cox's regression model. Variables that met this criterion were entered into the model in each stratum. Using a backward elimination strategy, those variables that retained a then significant independent association with adverse outcome ($P<0.05$) were included in the final model [18]. Model assumptions were checked graphically by log-minus-log versus time plots for each variable [16]. The computational work of Cox's regression model was performed using the EGRET (1991) software.

Results

A total of 148 children were included in the analysis. The median time of admission at protocol was 15 days and 82% of the children were admitted by 1 month of life. Median follow-up was 39 months. Sixteen patients (11%) had an adverse outcome: 11 patients (7%) died and 13 (9%) developed chronic renal failure. Death was associated with renal failure: of 13 patients with renal failure 8 died (relative risk =27, $P<0.001$).

Univariate analysis (Table 1)

In the prenatal echography stratum, all variables were significantly associated with adverse outcome. The presence of other sonography findings besides hydronephrosis was significantly associated with adverse outcome. These variables were presence of megacystis, megaureter,

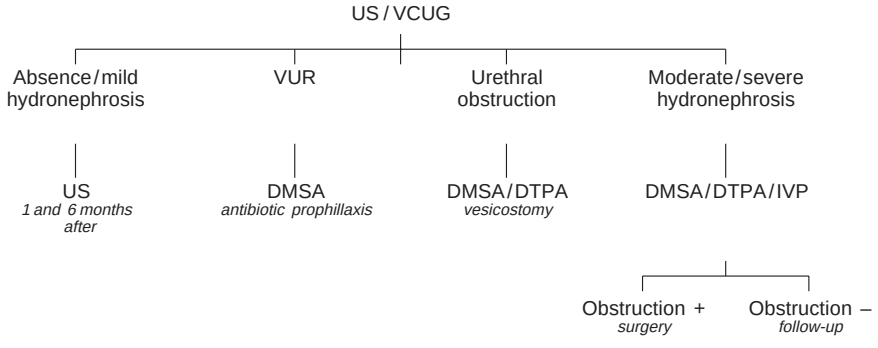

Fig. 1 Simplified algorithm for neonatal evaluation of prenatally detected hydronephrosis [*US* ultrasonography, *VCUG* voiding cystourethrogram, *VUR* vesicoureteral reflux, *DMSA* ^{99m}technetium (Tc)-dimercaptosuccinic acid scan, *DTPA* ^{99m}Tc-diethylene triamine penta-acetic scan, *IVP* intravenous urogram]

Table 1 Univariate analysis of prognostic factors among children with fetal hydronephrosis (*GFR* glomerular filtration rate)

	Adverse outcome (+) (*n*=16)	Adverse outcome (–) (*n*=132)	Log-rank	*P*
Prenatal echography				
gestational age at diagnosis				
second trimester	7	15	13	0.001
third trimester	9	117		
bilateral findings				
present	14	43	19	0.001
absence	2	89		
megaureter				
present	9	25	11.9	0.001
absent	7	107		
megacystis				
present	11	14	40.4	0.001
absent	5	118		
cysts				
present	4	1	76.3	0.001
absent	12	131		
oligohydramnios				
present	9	5	71.8	0.001
absent	7	127		
Clinical findings				
sex				
male	13	90	1	0.30
female	3	42		
race				
white	12	88	0.5	0.47
non-white	4	44		
birth weight				
<2500 g	9	17	21.7	0.001
>2500 g	7	115		
prematurity				
present	10	19	24.3	0.001
absent	6	113		
Apgar score 1 min				
<7	9	17	22	0.001
≥7	7	115		
Apgar score 5 min				
<7	5	4	29.1	0.001
≥7	11	128		
systolic pressure				
>90 mmHg	2	9	0.86	0.35
≤90 mmHg	14	123		
abnormal palpable kidney				
present	12	30	20.7	0.001
absent	4	102		
Initial laboratory findings				
urea				
≥25 mg/dl	14	22	40.6	0.001
<25 mg/dl	2	110		
creatinine				
≥0.9 mg/dl	11	6	84	0.001
<0.9 mg/dl	5	126		
GFR				
≤20 ml/min	9	4	70.6	0.001
>20 ml/min	7	128		
hematuria				
present	5	6	16.6	0.001
absent	11	126		
proteinuria				
present	5	5	15	0.001
absent	11	127		
bacteriuria				
present	1	5	0.15	0.7
absent	15	127		
pyuria				
present	1	7	0.005	0.94
absent	15	125		

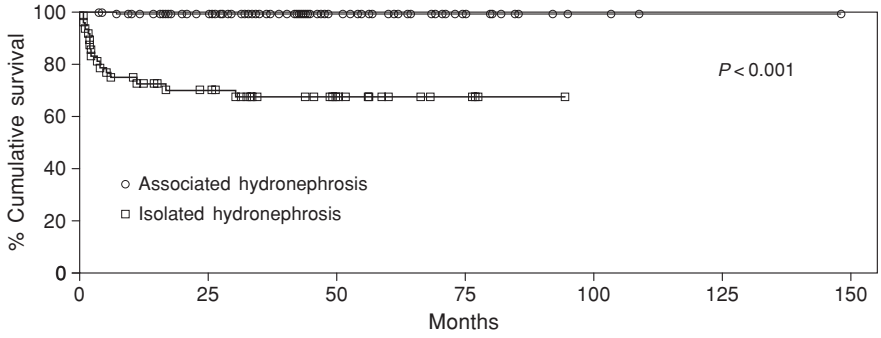

Fig. 2 Cumulative survival (Kaplan-Meier estimates) without adverse outcome comparing children with isolated fetal hydronephrosis and those with associated fetal hydronephrosis

Table 2 Multivariate analysis of adverse outcome in fetal hydronephrosis: final model (*CI 95%* 95% Confidence interval)

Variable	Coefficient	Standard error	Hazard ratio	CI 95%	*P*
Oligohydramnios	1.612	0.685	5	1.3–19	0.02
Prematurity	1.320	0.579	3.8	1.2–11	0.02
GFR ≤20 ml/min	1.850	0.664	6.3	1.7–23	0.005

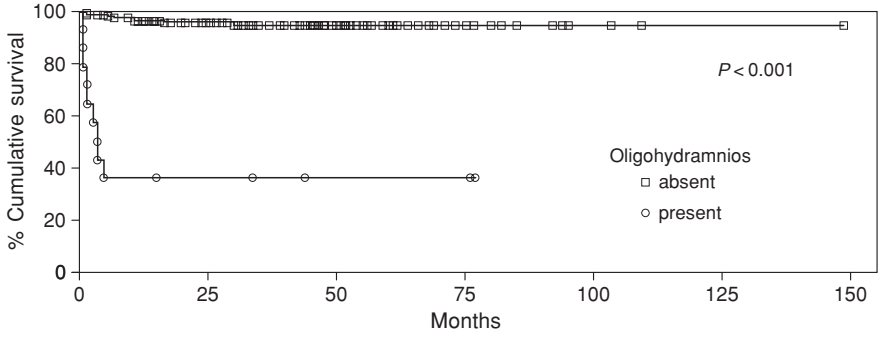

Fig. 3 Cumulative survival (Kaplan-Meier estimates) without adverse outcome comparing children with fetal hydronephrosis associated with oligohydramnios and those without oligohydramnios

cysts, oligohydramnios, and bilateral findings. In contrast, prenatal echography detection of isolated hydronephrosis, even bilateral, was associated with a protective effect. Estimated probability of survival without adverse outcome for patients with isolated hydronephrosis was 99%±1%. Conversely, the estimated probability of survival for patients with associated hydronephrosis was 67%±7% ($P<0.001$). The protective effect of isolated hydronephrosis is illustrated in Fig. 2.

In the clinical stratum, patients with adverse outcome had significantly lower birth weight and Apgar scores. Prematurity and abnormal palpable kidney were also significantly associated with adverse outcome. In the laboratory stratum, urea higher than 25 mg/dl, creatinine higher than 0.9 mg/dl, a glomerular filtration rate lower than 20 ml/min, presence of hematuria, and proteinuria were significantly associated with adverse outcome.

Multivariate analysis

The Cox regression model was used for each stratum. Seven variables remained significant after backward elimination by the regression model. In the prenatal echography stratum, two variables were independently associated with adverse outcome: oligohydramnios [hazard =10.5, 95% confidence interval (CI95%) =3.6–30] and bilateral findings (hazard =6.2, CI95% =1.3–30). In the clinical stratum, three variables remained as independent predictors of adverse outcome: prematurity (hazard =3.8, CI95% =1.3–10), 5-min Apgar score (hazard =8.5, CI95% =2.7–27), and abnormal palpable kidney (hazard =6.8, CI95% =2–22). In the laboratory stratum, two variables were independently associated with adverse outcome: urea higher than 25 mg/dl (hazard =13.9, CI95% =2.8–67) and glomerular filtration rate lower than 20 ml/min (hazard =6.5, CI95% =2.2–19).

Final model (Table 2)

All seven variables that remained independently associated with adverse outcome in each stratum were included in the final model. After adjustment, only three variables were found to be independent predictors of adverse outcome: presence of oligohydramnios (hazard =5, CI95% =1.3–19), prematurity (hazard =3.8, CI95% =1.2–11), and glomerular filtration rate lower than 20 ml/min (hazard =6.3, CI95% =1.7–23). Table 2 shows the final model with the three variables that remained as independent predictors of death or chronic renal failure in patients with fetal hydronephrosis. Interaction was assessed by

including the product terms in a final model, but all of these terms could be eliminated without contributing to the model.

Therefore, in each stratum there was one variable independently associated with adverse outcome. The estimated probability of survival without adverse outcome in the presence of oligohydramnios was 36%±12% compared with a probability of 95%±2% for those without oligohydramnios on prenatal echography ($P<0.001$). The influence of oligohydramnios on the duration of survival without adverse outcome is illustrated in Fig. 3. The estimated probability of survival without adverse outcome in the presence of prematurity was 65%±9% compared with a probability of 95%±2% for term newborns ($P<0.001$). The estimated probability of survival was 34%±11% for the patients with a glomerular filtration rate lower than 20 ml/min and 94%±1% ($P<0.001$) for those with a glomerular filtration rate higher than 20 ml/min.

Discussion

Prognostic studies allow the development of rational strategies for treatment/management of untoward consequences in persons who have the condition under study. Knowledge of the clinical course of a disease becomes particularly important in decisions regarding the best management. Management options for the fetus with hydronephrosis range from observation, with definitive evaluation at birth, to prenatal surgical intervention [6]. Other approaches to management are induction of premature labor to allow early correction of the anomaly and termination of pregnancy. However, with current knowledge, it is probably more beneficial to the infant to plan and arrange for appropriate postnatal management [19]. Postnatally, early prophylactic antibiotics and proper urinary tract investigation may reduce morbidity.

Previous studies have shown factors associated with a poor prognosis in fetal hydronephrosis. Nevertheless, studies of prognostic factors have been limited to cases in which prenatal intervention is considered [20, 21]. Besides, the majority of these studies applied univariate analysis and did not adjust for covariates [9, 10, 22]. Reinberg et al. [22] evaluated the clinical outcome of eight patients with prenatally detected posterior urethral valves and documented that oligohydramnios, postnatal respiratory insufficiency, and a nadir creatinine level in the 1st year of life higher than 1.2 mg/dl are predictive of progressive renal failure. In a series of cases of prenatally diagnosed posterior urethral valves, Hutton et al. [9] reported that detection at or before 24 weeks of gestation predicts a poor outcome. Recently, the same authors [10] reported a statistically significant association between poor outcome and marked second trimester hydroureteronephrosis with increased echogenicity or cystic change in the renal parenchyma. However, all of these studies performed univariate analyses that did not evaluate the combined effects of two or more factors.

Our study supports previously established univariate associations between various predictors and adverse outcome in fetal hydronephrosis. However, in multivariate analysis, after adjustment for the presence of other factors, only three variables remained as independent predictors of poor outcome: oligohydramnios, prematurity, and glomerular filtration rate lower than 20 ml/min.

Oligohydramnios is strongly associated with an adverse outcome [23], with perinatal mortality ranging from 70% to 100% in cases of fetal hydronephrosis with associated oligohydramnios [24, 25]. Dumez et al. [26] reported that the presence of oligohydramnios had a sensitivity of 71% and a specificity of 92% in predicting perinatal death in fetal hydronephrosis. Prematurity can contribute to an adverse outcome, due to additional morbidity associated with this condition. Thus, the theoretical benefits of premature delivery must be set against worse outcome for these newborns, and induction of premature labor should be viewed with caution. Another variable independently associated with adverse outcome in our study was a glomerular filtration rate lower than 20 ml/min. Other studies have shown that initial abnormal renal function in children with prenatally detected posterior urethral valves was significantly correlated with final renal function [26, 27].

The clinical applicability of prognostic models depends on feasible variables in their construction [28]. We considered only variables that are readily available in clinical practice. Unfortunately, other important variables, such as degree of hydronephrosis and parenchymal echogenicity on prenatal ultrasonography, were not available to us. We are currently planning a new prospective study including these variables.

In conclusion, we report a multivariate analysis of prognostic factors in fetal hydronephrosis. This analysis was derived from Cox's regression model, relying on data that are readily available to the clinician and are simple to obtain. The model allows for an objective assessment of the risk of death or serious morbidity and can be used for counselling the patient's family. The model identified that the combination of three factors – oligohydramnios, prematurity, and initial abnormal renal function – best predicts an adverse outcome. Thus, the present study shows that in pregnancies with oligohydramnios, the baby should be delivered at a tertiary care center to allow prompt evaluation. Prematurity and initial abnormal renal function also independently predicts poor outcome. Nevertheless, the clinical course of prenatally detected hydronephrosis has not been well defined. Prospective studies using survival analysis and multivariate model, including factors such as bladder wall thickness and degree of hydronephrosis are still necessary to select the best approach for management of the fetus and the neonate.

Acknowledgements This study was partially supported by Fundação de Amparo a Pesquisa do Estado de Minas Gerais (FAPEMIG), Conselho de Desenvolvimento Científico e Tecnológico (CNPq), and Pró-Reitoria de Pesquisa-UFMG. R.B.B. Oliveira and A.S. Vilasboas were recipients of CNPq and FAPEMIG fellowships.

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