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Petersen, Karen Lavinia

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THE OUTCOME OF POSTERIOR URETHRAL VALVES: A TWENTY-ONE YEAR EXPERIENCE.

Karen Lavinia Petersen

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfillment of the requirements for the degree

of

Master of Medicine in the branch of Paediatrics.

Johannesburg, 2008

I, Karen Lavinia Petersen, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the branch of Paediatrics in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

27th day of November, 2008

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This work is dedicated to my parents,

William and Patricia Petersen

who taught me the value of perseverance,

and to Professor Ella Hartman

an exceptional teacher and clinician

who planted the seed of possibility.

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Presentations arising from this study

Petersen KL, Faller G, Kala UK. The outcome of posterior urethral valves: a twenty-one year experience.

Poster presentation: South African Congress of Nephrology, Durban, 26- 29 July 2008.

Poster presentation: Faculty Research Day, University of the Witwatersrand. 20 August 2008.

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Abstract

Background: Posterior urethral valves (PUV) result in a spectrum of obstruction, and up to thirty percent of patients progress to renal failure.

Objective: Descriptive study of patients with PUV, and to compare growth and renal function in the primary valve ablation versus vesicostomy group.

Methods: Retrospective record review of patients with PUV at Chris Hani Baragwanath Hospital from January 1985 to December 2005.

Results: A total of 128 boys were identified. The mean (range) age was 12.9 months (0 to 139.4). The mean duration of follow-up was 42 months, with 65% lost to follow- up. UTI and voiding problems were the most common modes of presentation. Young age at presentation and renal dysfunction after surgery were poor prognostic features. Hydronephrosis was present in 89.5%. Renal failure was present in 37% of patients at last visit. Primary valve ablation was performed in 44.2% and vesicostomy in 55.8%. No statistical difference in renal outcome or somatic growth was observed between the surgical groups.

Conclusion: PUV is a common condition with significant morbidity. The renal outcome in black South African boys is similar to reports from developed countries. The type of initial surgical management did not impact on renal outcome or somatic growth.

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WitsETD

TABLE OF CONTENTS

	Page
DECLARATION	ii
DEDICATION	iii
PRESENTATIONS	iv
ABSTRACT	v
ACKNOWLEDGEMENTS	vi
TABLE OF CONTENTS	vii
LIST OF FIGURES	x
LIST OF TABLES	xi
GLOSSARY OF TERMS	xii
1.0 INTRODUCTION	1
1.1 Diagnosis of PUV	1
1.2 Clinical presentation	2
1.3 Management options	2
1.4 Renal outcome	3
1.5 Somatic growth	4
1.6 Aims of the study	5
2.0 MATERIALS AND METHODS	7
2.1 Ethics clearance	7

WitsETD

Page

2.2 Study design and sample 7

2.3 Diagnosis of posterior urethral valves 8

2.4 Renal function and serum electrolytes 8

2.5 Somatic growth 10

2.6 Statistical analysis 10

2.7 Limitations of the study 10

3.0 RESULTS 11

3.1 Population parameters 11

3.2 Clinical parameters 12

3.3 Radiological parameters 14

3.4 Surgical intervention 14

3.5 Renal outcome 15

3.5.1 Factors affecting renal outcome 15

3.6 Somatic growth 19

3.6.1 Age at presentation 21

3.6.2 Type of surgery 22

4.0 DISCUSSION 25

4.1 Descriptive analysis 25

4.2 Comparative analysis 27

WitsETD

Page

4.2.1 Renal outcome 27

4.2.2 Renal protective factors 28

4.2.3 Somatic growth 29

5.0 CONCLUSION 32

5.1 Recommendations 33

APPENDIX A Ethics clearance certificate 34

APPENDIX B Data collection sheet 35

REFERENCES 37

WitsETD

LIST OF FIGURES

Figure		Page
1.	VCU	1
2.	Age groups at presentation	11
3.	Mean GFR vs type of surgery in neonates	16
4.	Scatter plot for final GFR and GFR post- surgery	18
5.	Mean GFR vs age at presentation	18
6.	Mean length z- score vs age at presentation	22
7.	Mean weight z- score vs age at presentation	22
8.	Overall mean z- score for length vs type of surgery	23
9.	Neonatal group mean z- score for length vs type of surgery	23
10.	Overall mean z- score for weight vs type of surgery	24
11.	Neonatal group mean z- score for weight vs type of surgery	24

witsETD

LIST OF TABLES

Table		Page
1.	Clinical findings at presentation	12
2.	UTI organisms	12
3.	Co- morbid conditions	13
4.	Type of surgery vs age at presentation	14
5.	CKD stage at final visit	15
6.	Linear regression analysis for final GFR overall	17
7.	Linear regression analysis for final GFR in age groups 1 & 2	17
8.	CKD stage vs serum sodium	19
9.	Linear regression analysis for final length z- score	20
10.	Linear regression analysis for final weight z- score	21

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GLOSSARY OF TERMS

CKD: chronic kidney disease

DMSA: 99 technetium dimercaptosuccinic acid

GFR: glomerular filtration rate

PUV: posterior urethral valves

UTI: urinary tract infection

VCU: voiding cystourethrogram

VUR: vesico- ureteric reflux

VURD: valves with vesico- ureteric reflux and ipsilateral renal dysplasia

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CHAPTER 1

1.0 Introduction

Posterior urethral valves (PUV) result from a congenital malformation of the male urethra at the junction of the membranous and penile urethra that causes obstruction to urinary flow [1]. It is estimated to affect 1:5000- 1:8000 male births [2]. The exact embryology of PUV formation remains in dispute [3], and genetic abnormalities have been explored [4].

1.1 Diagnosis

The diagnosis may be suspected on antenatal ultrasound in the presence of oligohydramnios, hydronephrosis and a dilated proximal urethra with a resultant "keyhole" sign, but this is not specific for PUV [5]. The diagnosis must be confirmed after birth by voiding cystourethrogram (VCU), where the typical finding is that of a dilated posterior urethra with a trabeculated bladder [6] (Figure 1). Vesico-uretric reflux (VUR) may be present.

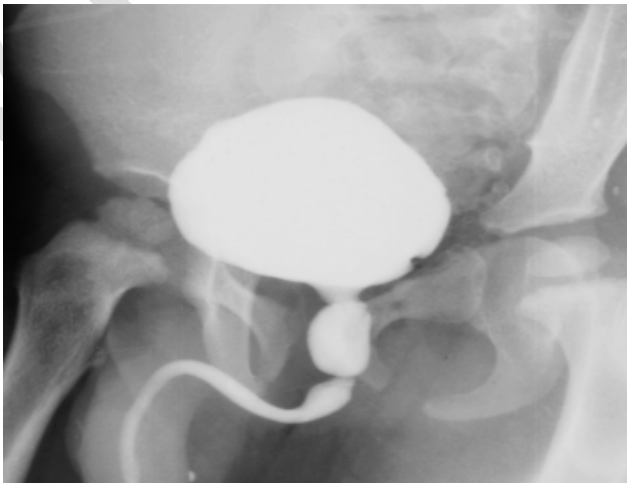


Figure 1. VCU showing a dilated posterior urethra. No VUR is present.

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The presence of PUV may also be confirmed at cystoscopy, when valves or remnants of valves are visible.

1.2 Clinical presentation

The clinical presentation of boys with PUV represents a spectrum of obstruction. Patients with severe obstruction present early in the neonatal period with Potters sequence of oligohydramnios: intra-uterine growth retardation, typical facies, pulmonary hypoplasia and renal dysfunction. They typically have hydronephrosis and a palpable walnut-shaped bladder. Patients with PUV may have ascites, metabolic acidosis, and/ or urosepsis [7, 8]. Milder forms of obstruction present later, usually with urinary tract infection (UTI), poor urinary stream or urinary incontinence [9].

1.3 Management options

Fetal surgery for PUV includes vesico-amniotic shunting or cystoscopy and valve ablation [2]. Theoretically, the relief of obstruction to urine flow should not only increase amniotic fluid volume to allow normal lung development, but it should also prevent renal dysfunction. However, in practice this is not the case [10, 11]. This could reflect primary renal dysplasia associated with PUV.

All patients with PUV are initially catheterized to overcome the obstruction, and carefully monitored for post- obstruction polyuria. Adequate intravenous fluid support is mandatory. Antibiotics are given if UTI or sepsis is suspected. Abnormalities of electrolytes and acidosis are corrected [12].

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The current surgical treatment of PUV is primary valve ablation via trans-urethral cystoscopy [13]. This procedure may be limited technically by resectoscope size, a problem overcome by the use of laser ablation if available, where a small diameter fiber is employed [14].

If primary ablation is not possible, temporary urinary diversion is achieved by vesicostomy, ureterostomy or nephrostomy, with valve ablation later when the urethra can accommodate the resectoscope. Some centers advocate diversion procedures for patients whose renal function has not improved despite catheterization [15, 16]. High diversion procedures may complicate with ureteric stricture formation and worse bladder capacity due to non-cycling of the bladder[17]. Vesicostomy, on the other hand, may result in a small capacity hyperreflexic bladder when compared to primary valve ablation [18]. The timing of urodynamic testing after surgery is important, as bladder compliance may change with time.

Although the obstruction is easily corrected, the effects of pressure on both upper and lower renal tract may be permanent. The term valve- bladder syndrome describes persistent hydroureteronephrosis after valve ablation [19]. Patients present with urinary incontinence due to bladder dysfunction, often worsened by nephrogenic diabetes insipidus with large volumes of dilute urine. The urodynamic findings include bladder hypertonia, detrusor hyperreflexia and/ or myogenic failure [20].

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1.4 Renal outcome

Although antenatal diagnosis has improved mortality, the long term renal outcome remains poor, with as many as 30% of patients progressing to renal failure [11].

To improve this outcome, many studies have attempted to identify good prognostic features and optimal surgical treatment. There seems to be no dispute that low serum creatinine after intervention carries a good renal prognosis [16, 21- 23], or that bladder dysfunction may be associated with poor long-term renal outcome [24, 25]. However, there has been conflicting results regarding age at presentation [23, 26, 27], pressure "pop-off" mechanisms such as unilateral VUR, ascites and bladder trabeculation [11, 28- 31] , and type of surgical intervention [32- 35].

1.5 Somatic growth

Poor somatic growth has been associated with increased mortality [36]. Somatic growth in children with PUV may be affected by many factors, including:

- Nutrition, which depends on both food availability and appetite [37- 39]
- Renal dysfunction [37, 40] , with associated abnormalities of parathyroid hormone (PTH) [41] , and metabolic acidosis [42]
- The presence of VUR [35]
- Type of surgery performed [43] and
- Renal salt wasting [44].

Although the measurement of growth in children is standard, the interpretation in

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children with renal dysfunction is difficult [45]. Using length to monitor growth is a more sensitive marker in children with renal failure [37]. In a child with fluid overload due to renal failure, weight may overestimate growth.

1.6 Aims of the study.

A twenty- one year follow-up of patients with posterior urethral valves enabled a descriptive study of the following parameters:

a) Age at presentation

b) The proportion of antenatal diagnoses

c) Clinical presentation

d) Radiological findings

e) Mortality

f) Renal outcome

g) Factors affecting renal outcome, specifically age at presentation, ascites and VURD.

In addition, this study compared the outcomes of boys treated with primary valve ablation versus vesicostomy with respect to the following parameters:

1) Glomerular filtration rate (GFR), calculated using the Schwartz formula [46]

2) Growth, using z-scores for weight and height/ length.

The outcome of PUV in black South African children has not been documented before. Primary valve ablation is the surgery of choice, but only possible if a small resectoscope

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is available. If not, a vesicostomy is performed with valve ablation at a later stage when the urethra can accommodate the available resectoscope.

Since the choice of surgery depended entirely on the availability of a suitable resectoscope and not on the state of the upper renal tract or renal function, this study population provided a unique opportunity to compare growth and renal outcome in patients with similar renal status who had different surgical treatments.

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CHAPTER 2

2.1 Ethics clearance

Ethics clearance was obtained from the Human Research and Ethics Committee of the University of the Witwatersrand; clearance number M070206 (appendix A).

2.2 Study design and sample

This was a retrospective record review of patients diagnosed with PUV and followed-up by the paediatric renal unit from January 1985 to December 2005 at Chris Hani Baragwanath Hospital. This is a large teaching hospital attached to the University of the Witwatersrand providing primary, secondary, tertiary and quaternary care to the people of Gauteng and to patients referred from other provinces and African countries. Records of all patients diagnosed with PUV during the study period were retrieved from the renal clinic filing system. Data was collected as per data sheet (appendix B). Patients were divided into four groups depending on their age at presentation:

- Group 1: age less than one month
- Group 2: age one month to twelve months
- Group 3: age more than twelve months to sixty months
- Group 4: age more than sixty months.

For comparative analysis of surgery, patients were categorized into a primary valve ablation group and a vesicostomy group.

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Visits were defined as follows:

1. initial visit: at presentation to hospital
2. post- surgery visit: approximately 6 months post initial surgery
3. final visit: last visit documented in the renal file before 31 December 2005.

2.3 Diagnosis of PUV

Posterior urethral valves were diagnosed either with VCU or cystoscopy. The presence of secondary VUR on VCU was graded using the International Reflux Study Group grading system [47]. Also, most patients had abdominal ultrasound examinations as an initial investigation, where the presence or absence of hydronephrosis and ascites was documented.

2.4 Renal function and serum electrolytes

Serum creatinine was measured by the National Health Laboratory System (NHLS) using a Roche Hitachi automated clinical chemistry analyzer. This system uses the modified Jaffe reaction and is a kinetic in vitro test. The GFR was calculated using the formula [46], GFR= *k x* length (cm) x 88.5 / serum creatinine (umol/l), where *k* is an age and sex specific constant; *k*= 0.33 for low birth weight infants, *k*= 0.45 for infants less than 1year, *k*= 0.55 for children up to 12 years, and *k*= 0.70 for boys older than 12 years of age. This calculated GFR value was compared to age- appropriate tables of mean GFR to classify renal function as normal or decreased [48]. In six records where patient height was not available, the expected height for age was used to calculate GFR. Although the estimated GFR may have been falsely raised in these patients, the calculated GFR is preferred to

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serum creatinine as a marker of renal function since it includes patient height and gender in the equation. The calculated GFR at final visit was categorized into five stages using the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines for the Classification of Chronic Kidney Disease [49].

In addition, most patients had radioisotope 99m Technetium dimercaptosuccinic acid (DMSA) scans performed to assess differential kidney function, the results of which were useful in deciding on nephrectomy for patients who had severe VUR in a non-functioning kidney and recurrent pyelonephritis. Valves with vesico-ureteric reflux and renal dysplasia (VURD) was defined as unilateral grade 4-5 VUR with ipsilateral renal dysplasia as evidenced by split function on DMSA scan of less than ten percent [29].

Sodium in plasma or serum was determined by the NHLS electrochemically with a Na+ - ISE. Hyponatraemia was defined as a serum sodium concentration of less than 130mmol/l [50]. Hypernatraemia was defined as a serum sodium concentration of more than 150mmol/l [51].

Serum or plasma total carbon dioxide was determined by the NHLS enzymatically using phosphoenolpyruvate carboxylase on Roche automated clinical chemistry analyzers. The normal reference value for venous plasma or serum bicarbonate (HCO_3^-) for children is 22-29 mmol/l, and 20- 22 mmol/l for term newborns[52] . Metabolic acidosis was defined as measured total carbon dioxide level of less than 20mmol/l.

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2.5 Somatic growth

The weight in kilograms and height or length in centimeters was documented for each visit. Z-scores were calculated for weight for age and height/ length for age using epi-info anthropometric calculator, CDC 2000 growth charts [53].

2.6 Statistical analysis

All information was captured and analysed using epi- info version 2002. The analysis was confirmed using Stata statistical package. The students' t-test was used to analyse quantitative variables. For categorical variables the chi- squared test was used. A *p* value of less than 0.05 was considered statistically significant. Regression analysis was used to find correlation factors for final GFR and somatic growth.

2.7 Limitations of the study

The following limitations of this retrospective study were anticipated:

1. Neonates with severe obstruction and dysplastic kidneys may have demised before a diagnosis was established.
2. Patients managed by urologists or surgeons may not have been referred to the renal service if they had normal renal function at presentation.
3. Some data may be missing if not documented by the attending paediatrician.
4. Measurement of weight and height/ length was not standardized.

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CHAPTER 3

3.0 Results

A total of 128 patients were identified. All patients were of African descent. Eight records were excluded from analysis (3 refused consent to surgery, 3 had upper tract diversion, and 2 files could not be traced).

3.1 Population parameters

Figure 2 shows the percentage of patients in each of the 4 age groups at presentation.

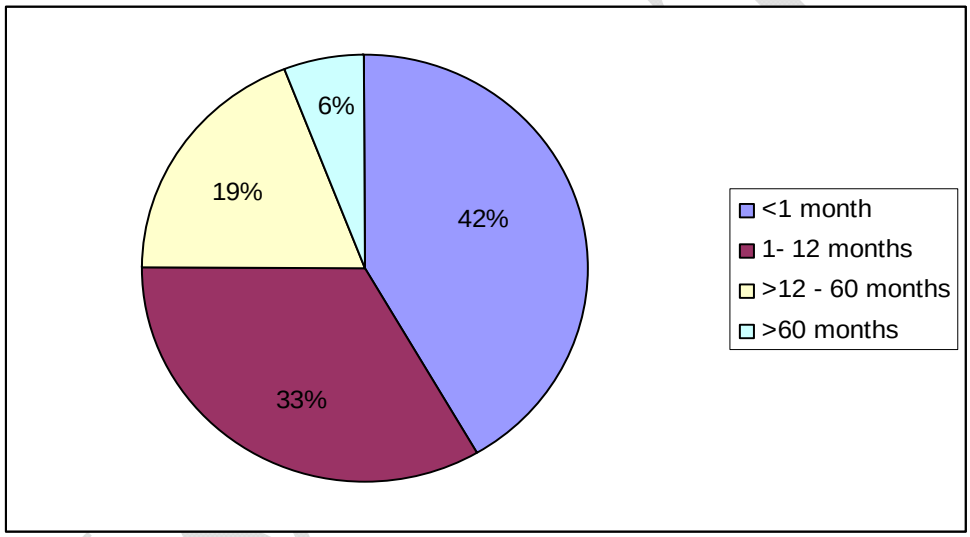


Figure 2: Age groups at presentation

Ninety patients (75%) presented in the first year of life; 42% as neonates and 33% aged 1- 12 months. Thirty patients presented after the age of 12 months. The mean (range) age at presentation was 12.9 (0 to 139) months. The mean (range) duration of follow-up was 42 (1 to 206) months. Seventy- eight patients (65%) were lost to follow- up, with a mean (range) duration of follow-up of 30.7 (1- 143) months. On average six new cases were

diagnosed every year. There were 5 (4.2%) documented deaths during the study period.

3.2 Clinical parameters

UTI and voiding problems were the most frequent mode of presentation. Voiding problems included delayed urination in the newborn period, poor urinary stream, dribbling of urine, and crying on micturition. Laboratory abnormalities included acidosis and hyponatraemia. Acidosis persisted in 53% of patients at the final visit. Jaundice was the presenting symptom in 12% of neonates. In five patients PUV were suspected at an antenatal visit (Table 1).

	n	Total	Percent
Acidosis	80	103	77.7
UTI	80	112	71.4
Voiding problems	55	101	54.5
Distended abdomen	45	98	45.9
Hyponatraemia	39	115	33.9
Ascites	22	114	19.3
Neonatal jaundice	6	50	12.0
Vomiting	9	120	7.5
Haematuria	7	120	5.8
Seizures	7	120	5.8
Antenatal diagnosis	5	120	4.2

Table 1: Clinical findings at presentation.

Organism	*n*	Percent
E coli	29	43.9
Klebsiella	15	22.7
Enterobacter	8	12.1
Proteus	3	4.5
Morganella	1	1.5
Serratia	1	1.5
A baumani	1	1.5
S aureus	4	6.1
E faecalis	2	3.0
Group B strep	1	1.5
C albicans	1	1.5
Total	66	100.0

Table 2: UTI organisms

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Organisms were documented in 66 of 80 (83%) patients who presented with a UTI; 58 of the 66 organisms identified were gram negative bacilli (Table 2).

Fifteen patients had abnormalities involving other systems, especially the urogenital and central nervous systems (Table 3). The study was not powered to determine whether these abnormalities were more frequent in patients with PUV than in the general population.

System affected	***n***	**Percent**	**Condition**	
Neurological	9	7.5	Spina bifida	1
			School failure	8
Urogenital	8	6.6	Cryptorchidism	4
			Patent urachus	2
			VUJ obstruction	1
			Inguinal hernia	1
Cardiovascular	5	4.2	ASD	1
			DORV, PS	1
			Mitral valve cleft	1
			Myocarditis	1
			VSD, PDA	1
Gastro-intestinal	2	1.7	Anorectal malformation	1
			Delayed gastric emptying	1
Total	**24**	**20**		**24**

Table 3: Co- morbid conditions

(VUJ vesico-ureteric junction; ASD atrial septal defect; DORV double outlet right ventricle; PS pulmonary stenosis; VSD ventricular septal defect; PDA patent ductus arteriosus).

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3.3 Radiological parameters

Abdominal ultrasound findings were available for 114 patients at presentation. Hydronephrosis was present in 102 (89.5%), bilateral in 94 and unilateral in 8. There was no hydronephrosis in 12 (10.5%) patients. Bladder abnormalities were not analysed.

VCU findings were documented in 102 patients. VUR was demonstrated in 36% of patients, unilateral in 24% and bilateral in 12%. VURD was diagnosed in 6 of 102 patients (5.8%). All 6 patients had nephrectomies performed.

3.4 Surgical intervention.

Fifty- three patients had primary valve ablation; mean (range) weight 9.4 (2.3- 41) kg, while vesicostomy was performed in 67 patients; mean (range) weight 3.6 (1.4- 12.2) kg. Younger patients were more likely to have a vesicostomy performed, $p<0.001$ (Table 4). This reflects the limited availability of small resectoscopes.

	< 1 month	**1-12months**	**>12-60months**	**> 60months**	**Total**
Primary ablation	6	19	21	7	**53**
Vesicostomy	44	21	2	0	**67**
Total	**50**	**40**	**23**	**7**	**120**

Table 4: type of surgery vs age at presentation

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3.5 Renal outcome

Table 5 shows the calculated GFR at final visit in the study group. Thirty-seven percent of patients had renal failure (calculated GFR < 60ml/min/1.73m^2) [49]. Renal failure was present at last visit in 35% of patients who did not return for scheduled visits. Six patients (5%) were referred for renal transplantation.

GFR (ml/min/1.73m^2)	***n*** **Total (percent)**	***n*** **Lost**	***n*** **Died**
> 90	53 (44.2)	35	0
60- 89	22 (18.3)	16	1
30- 59	23 (19.2)	16	2
15– 29	11 (9.2)	6	0
< 15	11 (9.2)	5	2
Total	120 (100)	78	5

Table 5: CKD stage at final visit

3.5.1 Factors affecting renal outcome

The effect of type of surgical procedure on GFR is best assessed in the neonatal group. This eliminates the confounding variables of age at presentation, kidney maturation, degree of obstruction and bladder dysfunction. Figure 3 shows the mean calculated GFR in the neonatal group at initial visit (p= 0.85), 6 months after the procedure (p= 0.67), and at final visit (p= 0.87) in the 2 surgical groups. There is no significant difference in final GFR for the surgical procedures. The mean (range) duration of follow-up in the neonatal group was 46.3 (1- 161) months.

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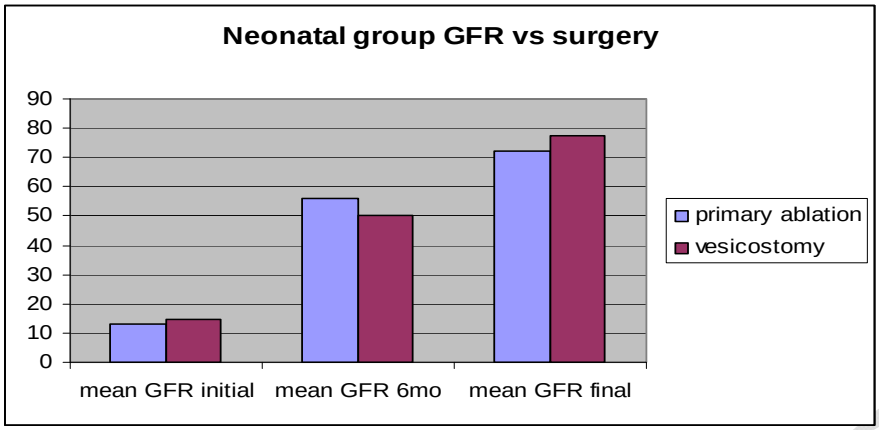


Figure 3: Mean GFR vs type of surgery in neonates

Linear regression analysis for all possible factors affecting final GFR was performed for the study group overall (Table 6) and for age groups 1 and 2 separately (Table 7). Group 2 was analysed separately since patient numbers were similar for the two surgical procedures. Age at presentation, bilateral irregular uptake on DMSA scan, and initial and post- surgery GFR, had a statistical significant impact on final GFR for all age groups. However, in both the neonatal age group and group 2, only the GFR post- surgery was significantly associated with the final GFR. Of note, the type of surgery performed, presence of ascites or VURD, and antenatal diagnosis did not impact on final GFR. Using multiple regression analysis, only GFR post- surgery was statistically significant. A scatter plot for final GFR was determined (figure 4).

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Variable	Overall, *n= 120*		
	co-efficient	**r^2**	***p*- value**
Antenatal diagnosis	-19.46	0.01	0.45
Age in months	1.04	0.12	**0.004**
Ascites	-24.35	0.05	0.42
DMSA irregular uptake	-33.38	0.11	**0.03**
GFR initial	0.75	0.25	**0.0001**
GFR 6months post surgery	0.72	0.40	**0.00001**
Surgery	-11.23	0.01	0.36
VUR	-29.68	0.03	0.28
VURD	-40.0	0.02	0.27

Table 6: Linear regression analysis for final GFR in group overall.

Variable	**Neonatal group ,** ***n= 50***			**Age group 2 ,** ***n= 40***		
	co-efficient	**r^2**	***p*- value**	**co-efficient**	**r^2**	***p*- value**
Antenatal diagnosis	-5.96	0.00	0.79	no antenatal diagnoses		
Age in months	17.61	0.02	0.477	3.46	0.04	0.4
Ascites	31.68	0.07	0.18	-37.25	0.07	0.56
DMSA irregular uptake	25.62	0.08	0.28	-44.75	0.16	0.24
GFR initial	1.345	0.08	0.167	0.64	0.20	0.055
GFR 6months post surgery	1.095	0.44	**0.0001**	0.96	0.44	**0.005**
Surgery	4.99	0.00	0.800	-1.20	0.00	0.963
VUR	-23.05	0.04	0.358	74.11	0.12	0.24
VURD	Unable to do, only 1 value			-33	0.02	0.63

Table 7: Linear regression analysis for final GFR in age groups 1 and 2

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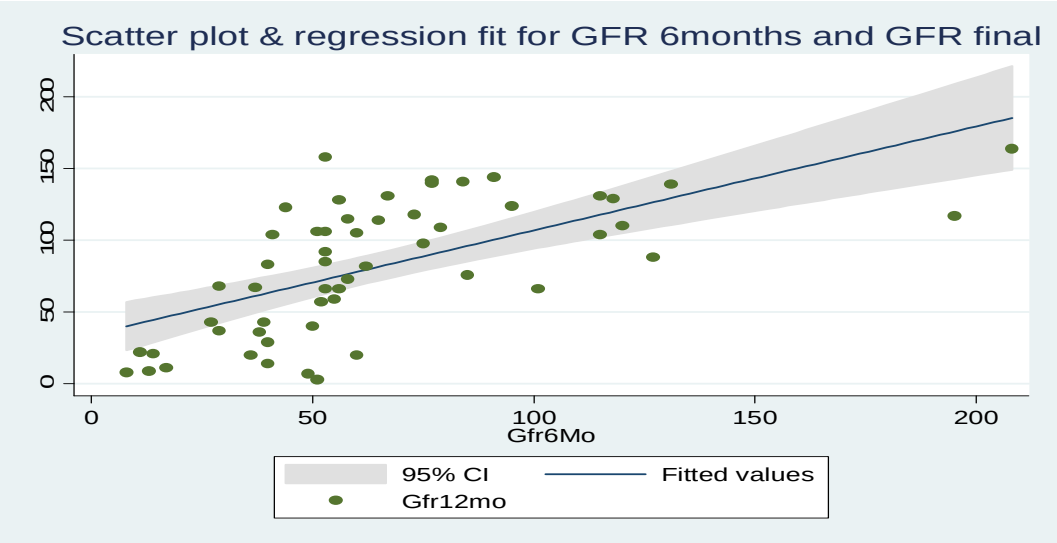


Figure 4: scatter plot for final GFR and GFR post surgery

Late age at presentation was associated with better initial and final GFR (figure 5).

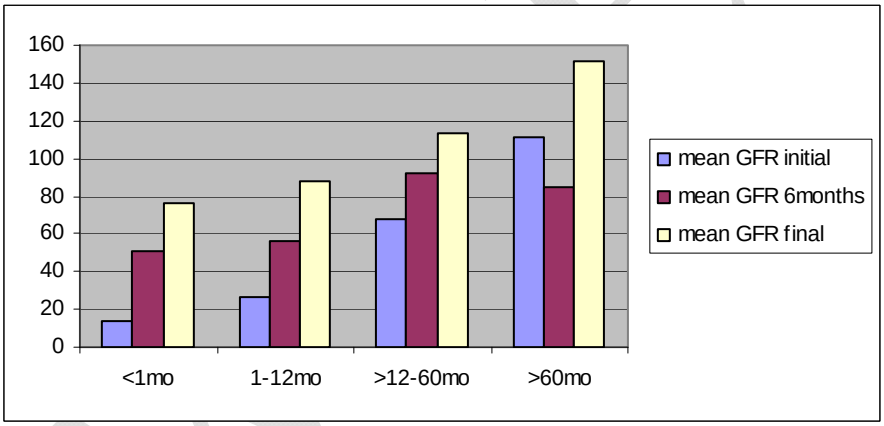


Figure 5: Mean GFR vs age at presentation

Patients who had normal serum sodium at presentation were more likely to have normal renal function at final visit, $p = 0.035$ (table 8).

	CKD STAGE					
serum sodium	**1 GFR>90**	**2 GFR 60-89**	**3 GFR 30-59**	**4 GFR 15-29**	**5 GFR <15**	**TOTAL**
decreased	9	10	8	5	7	39
Row %	23.1	25.6	20.5	12.8	17.9	100.0
Col %	18.0	45.5	36.4	50.0	63.6	33.9
increased	1	1	0	1	0	3
Row %	33.3	33.3	0.0	33.3	0.0	100.0
Col %	2.0	4.5	0.0	10.0	0.0	2.6
normal	40	11	14	4	4	73
Row %	54.8	15.1	19.2	5.5	5.5	100.0
Col %	80.0	50.0	63.6	40.0	36.4	63.5
TOTAL	50	22	22	10	11	115
Row %	43.5	19.1	19.1	8.7	9.6	100.0
Col %	100.0	100.0	100.0	100.0	100.0	100.0

Table 8: CKD stage vs serum sodium

3.6 Somatic growth

The following factors correlated with final height in all age groups (table 9): GFR at all study visits, initial and post- surgery z- scores for length, and bilateral irregular uptake on DMSA scan. In the neonatal group however, only 3 variables were significant: GFR at 6 months post surgery, final GFR, and z-score for length at 6 months post surgery. The age at presentation, type of surgery, and acidosis did not affect the final height.

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Variable	Overall, *n= 120*			Neonatal group, *n= 50*		
	Co-efficient	**r^2**	***p*- value**	**Co-efficient**	**r^2**	***p*- value**
Acidosis initial	-0.77	0.05	0.26	0.677	0.08	0.626
Acidosis 6mo	0.36	0.12	0.53	0.548	0.08	0.54
Acidosis final	-0.49	0.06	0.56	2.106	0.18	0.016
Age in months	0.02	0.04	0.07	2.08	0.09	0.08
GFR initial	0.01	0.09	**0.01**	0.044	0.04	0.325
GFR 6mo	0.02	0.25	**0.00003**	0.046	0.34	**0.001**
GFR final	0.027	0.48	**0.0001**	0.037	0.47	**0.000023**
Irregular uptake DMSA	1.73	0.15	**0.04**	2.185	0.18	0.06
Surgery	-0.57	0.02	0.17	-1.231	0.05	0.219
VURD	-0.125	0.00	0.89	Unable to do, only 1 value		
z- score length 6months	0.69	0.42	**0.001**	0.66	0.39	**0.000095**
z- score length initial	0.25	0.08	**0.01**	0.266	0.06	0.23

Table 9: Linear regression analysis for final length z- score

Similarly, table 10 shows the variables affecting final weight z- scores. For the overall group these include acidosis at final visit, age at presentation, GFR at all study visits, type of surgery, and initial and 6 months post- surgery z- scores for weight. For the neonatal group only 4 variables remained significant: acidosis at final visit, GFR after surgery, final GFR, and post surgery z-score for weight. Using stepwise regression analysis, only the initial and post- surgery z-scores for weight, and acidosis at final visit correlated with final weight z- scores.

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Variable	Overall, *n= 120*			Neonatal group, *n= 50*		
	co-efficient	**r^2**	***p*- value**	**co-efficient**	**r^2**	***p*- value**
Acidosis final visit	1.3	0.11	**0.004**	2.365	0.24	**0.0051**
Age months	0.025	0.06	**0.029**	1.364	0.04	0.243
GFR initial	0.01	0.07	**0.027**	0.053	0.05	0.255
GFR 6 months	0.023	0.23	**0.000053**	0.048	0.39	**0.00242**
GFR final	0.024	0.38	**0.000001**	0.036	0.46	**0.00002**
DMSA irregular uptake	0.713	0.12	0.102	1.730	0.16	0.116
Surgery	-0.962	0.06	**0.023**	-1.505	0.07	0.125
VURD	0.280	0.0012	0.776	Only 1 value, unable to do		
z- score weight initial	0.28	0.05	**0.047**	0.252	0.01	0.515
z-score weight 6month	0.72	0.50	**0.0001**	0.72	0.44	**0.00001**

Table 10: linear regression analysis for final weight z-score.

3.6.1 Age at presentation

The initial mean z-score for length and weight was relatively better in the neonatal group (figure 6 & 7), possibly reflecting adequate placental function as a determinant of fetal growth. The mean z-scores for length and weight then deteriorated at subsequent visits in this group. This could be due to a combination of factors, including renal dysplasia, acidosis and malnutrition. In all other age groups the mean z- scores for length and weight improved with time after intervention. Young age at presentation was associated with a less favourable final weight and height z- score. .

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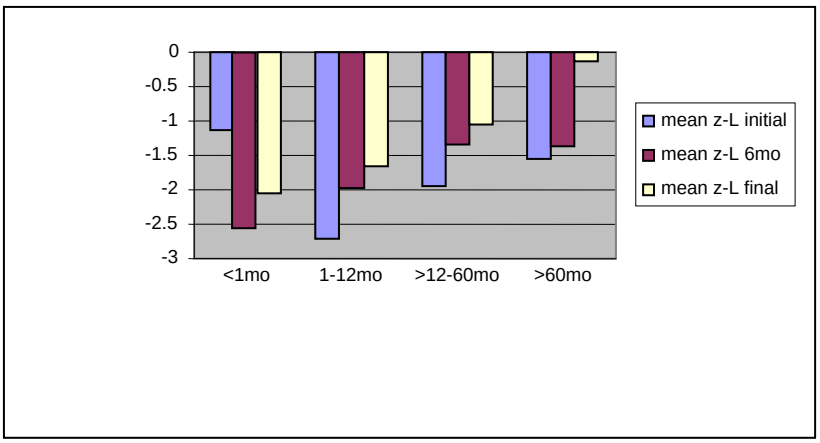


Figure 6: mean length z- score vs age at presentation.

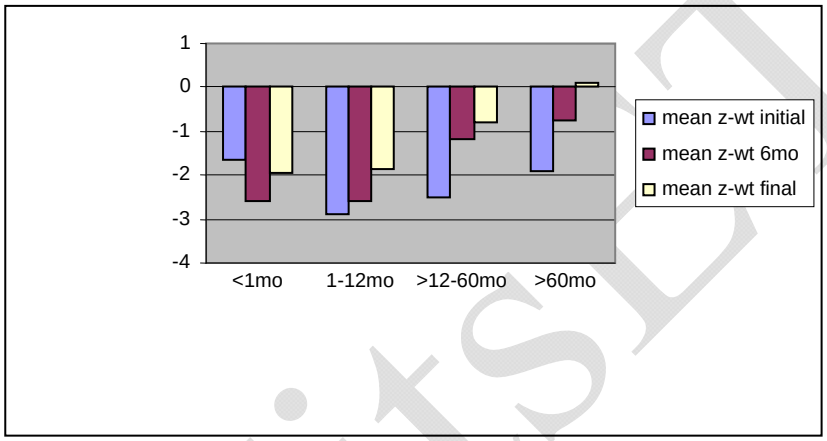


Figure 7: mean weight z- score vs age at presentation.

3.6.2 Type of surgery

Figure 8 shows the impact of type of surgery on mean length z- scores for all age groups. There was no statistical significant difference in z- scores in the 2 surgical groups, but the primary ablation group showed some improvement in mean z- scores for length. This different outcome was not reflected in the analysis of the neonatal group (figure 9). Analyses of the neonatal group eliminates the confounding variables of age at presentation and degree of obstruction.

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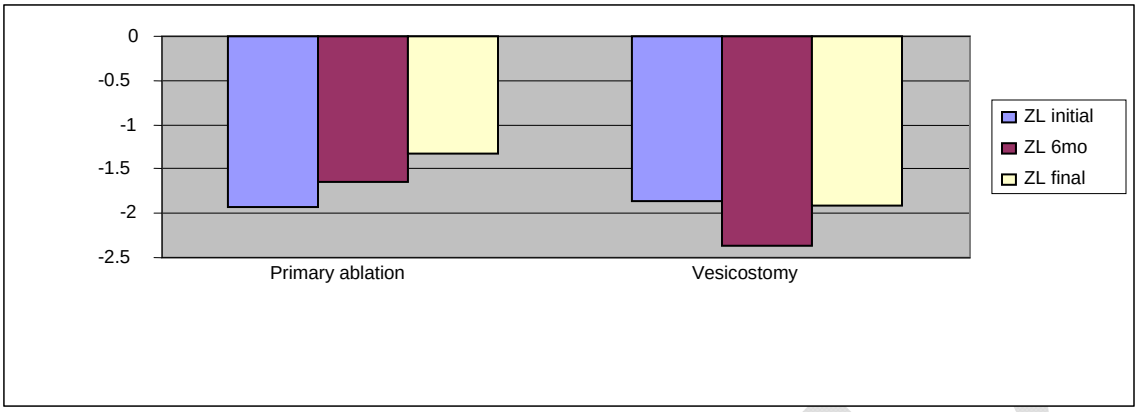


Figure 8: Overall mean z-score for length vs type of surgery

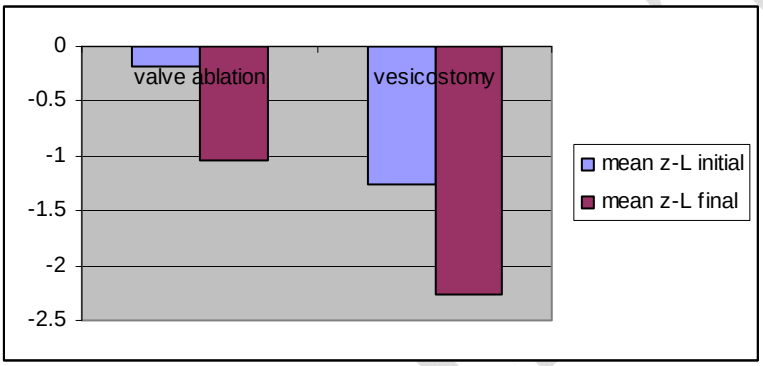


Figure 9: Neonatal group mean z-score for length vs type of surgery

Figure 10 shows the mean z- scores for weight in the 2 surgical groups. Overall, the final mean z-score for weight was significantly better in the primary valve ablation group, *p = 0.0014.* This did not reach significance in the neonatal group (figure 11).

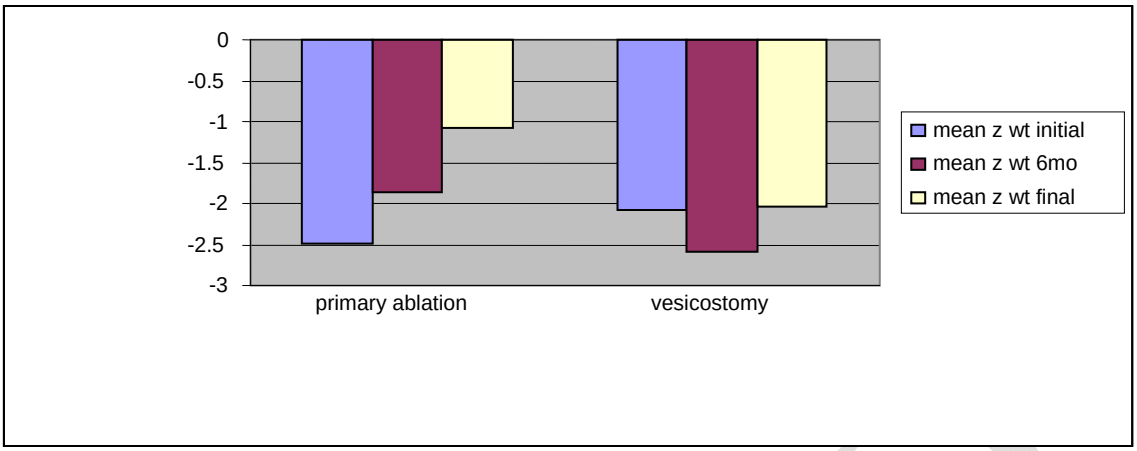


Figure 10: Overall mean z-score for weight vs type of surgery

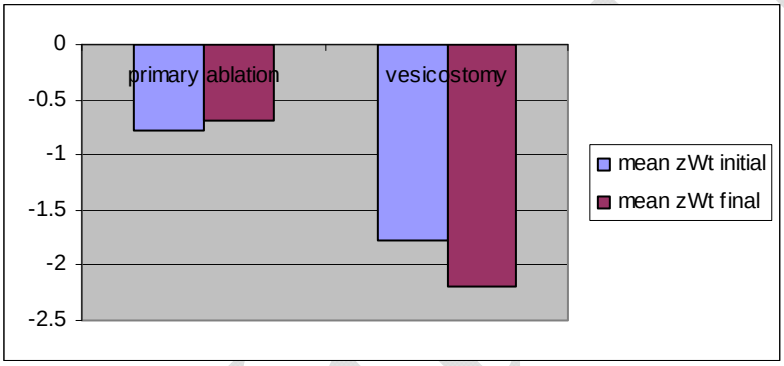


Figure 11: Neonatal mean z-scores for weight vs type of surgery

CHAPTER 4

4.1 Descriptive analysis

The results of the descriptive data are typical of a developing country [32, 54, 55].

The antenatal detection rate is low compared to the developed world; less than 5% of this cohort had antenatal detection compared to 41% in other reports [56]. Screening antenatal ultrasound examinations are not offered routinely to patients at Chris Hani Baragwanath Hospital or at the primary care maternity clinics attached to the hospital. Suboptimal staff to patient ratios limits this as an option. The mean age at presentation is one year of age, reflecting the low rate of antenatal detection. However, most patients were diagnosed with PUV within the first year of life.

A large proportion of patients do not return for scheduled clinic visits, especially after definitive surgery has been performed. This is concerning especially since some patients will progress to renal failure due to valve bladder syndrome, recurrent UTI, reflux nephropathy and hyperfiltration injury [15, 20, 21].

The mortality appears low (5 deaths), but this is not representative since 43 patients who did not return for scheduled visits had reduced GFR. It is possible that some of these patients died at home or in other centres.

The clinical presentation of this group of patients is similar to other reports, with UTI and voiding problems the most common mode of presentation. Metabolic acidosis persisted in

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more than half of the patients at last visit. The metabolic acidosis was not related to worsening GFR. This probably reflects a renal tubular acidosis. Patients are treated with sodium bicarbonate routinely if this is diagnosed. Poor adherence to medication or inadequate dosing could explain this finding.

Neonates commonly present with jaundice and/ or seizures. This could be a result of underlying urosepsis, electrolyte and metabolic derangements, and renal failure. A urine dipstix and culture is mandatory in such patients.

Abnormalities of other organ systems are frequent in this group of patients, especially involving the urogenital and neurological system. Whether this is more frequent than in the general population cannot be confirmed, but it could be in keeping with a congenital abnormality [13]. Patients should be screened for abnormalities in other systems. School failure is a common co- morbid condition and should be enquired about with appropriate referral for assessment. It is possible that school failure is a result of brain involvement as part of a congenital abnormality, or due to seizures, sodium abnormalities and/ or uraemia during the period of brain development, or due to poor self- esteem associated with urinary incontinence.

Hydronephrosis on abdominal ultrasound is not universal in patients with PUV; in this study hydronephrosis is absent in 10.5% of patients. In other studies hydronephrosis was documented in 47% to 80% of patients at presentation [9, 33, 55]. This could be explained by the theory that PUV has a spectrum of obstruction, and only cases with severe obstruction

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results in back pressure, VUR or relative vesico-ureteric junction obstruction due to a hypertrophied bladder. It is also possible that bladder catheterization drains the hydronephrosis so that this finding is not noticeable at the time of ultrasonography [19]. Krueger et al demonstrated hydronephrosis using intravenous pyelogram (IVP) in all their patients with PUV [43]. IVP is not routinely used in paediatric patients due to the risk of contrast and radiation exposure. It is possible that IVP is more sensitive than ultrasound in the detection of hydronephrosis. Also, although some ultrasound examinations are performed by sonographers and junior registrars, these are supervised and probably do not explain the cases without hydronephrosis. It is worth noting that this cohort had PUV diagnosed with VCU and/ or cystoscopy. The results of this analysis suggest that a normal abdominal ultrasound in a boy does not exclude the diagnosis of PUV in our population, and a VCU should be considered if a UTI is diagnosed in a boy.

VUR was demonstrated in 36% of patients at presentation. The frequency of VUR ranged from 16% to 80% in the literature reviewed [9, 11, 18, 21, 22, 24- 26, 29] . Where catheterization of the bladder was not possible, a retrograde urethrogram was performed; this may underestimate the true frequency of VUR in this study population.

4.2 Comparative analysis

4.2.1 Renal outcome

The renal outcome is similar to reports from developed countries [11]. Thirty- seven

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percent of patients have renal failure (GFR < 60ml/min/1.73m^2) at the final visit.

4.2.2 Renal protective factors

Overall, age at presentation was significantly associated with renal outcome, with older children having a relatively better calculated GFR at both the initial and final visits. Reports of poor renal survival in children who present before one year of age has been published before [23]. This is in contrast to other studies [26, 27] where late presentation resulted in a worse renal outcome. However, the late presentation group reported by El-Sherbiny et al [27] had more hydroureteronephrosis than the younger group, a confounding factor that may reflect valve bladder syndrome and its associated progression to renal failure. Ziylan et al [26] compared late presentation to a group who presented before age 5 years and found worse renal outcome in the late presentation group. Perhaps if they selected the young age group to include only children less than one year of age their findings would have been different. Older children may represent milder forms of obstruction. Late age at presentation should not be confused with delay in diagnosis.

VURD and ascites have been reported to offer protection against renal failure since it allows pressure pop-off mechanisms [28- 30]. This was not demonstrated in this analysis. However, numbers were small for VURD. Only six patients in this study population had VURD diagnosed, but ascites was documented in 22 (19.3%) patients. Other studies could also not demonstrate renal protection by VURD [11, 56]. In addition, scarring in the

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contralateral kidney has been documented on DMSA scan [57]. This carries with it the long- term risk of hypertension and renal failure.

The type of surgery performed and its impact on renal outcome was similarly assessed by others [33- 35]. Like this study, they demonstrated no difference in renal outcome for vesicostomy or primary valve ablation.

This study demonstrated a significant association between normal serum sodium at presentation and normal final renal function in 51 patients compared to 22 patients with normal serum sodium and renal failure. However, the reverse is not true. Of the 39 patients who had hyponatraemia, 19 had a calculated GFR > 60ml/min/1.73m2 and 20 had renal failure (GFR <60ml/min/1.73m2).

The post surgery GFR correlated well with the final GFR. A scatter plot was determined. This has been shown previously in other studies [11, 16, 23]. The creatinine at presentation should not be used to prognosticate renal outcome.

In summary: late age at presentation, normal GFR after surgery, and normal serum sodium at initial visit were favourable prognostic factors. The type of surgery performed and the presence of pressure pop- off mechanisms did not influence renal outcome.

4.2.3 Somatic growth

The following factors were associated with poor somatic growth in this study population:

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- Acidosis at last visit. This was associated with poor final z-score for weight but not for length. The acidosis was not related to renal failure and uraemia. It probably reflects a renal tubular acidosis. This has been described before in children with obstructive uropathy [21]. Acidosis limits growth due to non- pulsatile secretion of growth hormone [42].
- Age at presentation. Children who presented after the age of 12 months had relatively better initial and final z- scores for length. Similar findings were reported by Krueger et al [43] and Drozdz et al [23]. This is in keeping with previous suggestions that this group of children represents a milder form of obstruction. This late age at presentation should not be confused with delayed diagnosis of PUV.
- GFR at all study visits. Renal failure was associated with poor growth in this study population. Multiple factors may be responsible for this, including poor appetite, acidosis, anaemia, and uraemic gastritis [35, 37, 40].
- Irregular uptake on DMSA scan of both kidneys affected the final z- score for length in this study. Narasimhan et al [57] reported no difference in growth rate for children with and without renal scarring on DMSA scan. However, their group included patients with unilateral scarring only. It is possible that scarring involving only one kidney may not limit somatic growth to the extent that bilateral scarring does.
- Weight and height z- scores at all study visits correlated with the final z- scores for weight and height. This is not unexpected.

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- Type of surgery. Overall, children in the primary valve ablation group had significantly better final z- scores for weight than children in the vesicostomy group. However, the confounding factors are that the vesicostomy patients were smaller and younger, and may reflect a group with more severe obstruction and immature renal function. There was no difference in final z- scores for weight when type of surgery was compared in the neonatal group. The mean z- scores for weight and length improved in all groups after surgical and medical intervention. Krueger et al [43] showed a remarkable improvement in growth in a group of neonatal boys who had supravesical diversion compared to those with primary valve ablation, even though the former group had worse initial serum creatinine. They postulate that supravesical diversion allows greater preservation of nephron function. Their data however, does not include statistical analysis, so although they may show trends of improved growth in the supravesical diversion group, the statistical significance of this has not been proven. In this report, patients who had supravesical diversion procedures were excluded from analysis, so it is not possible to confirm or refute those findings.

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CHAPTER 5

5.0 Conclusion

PUV is common in this population with on average 6 new cases diagnosed per year. This is probably an underestimate for reasons discussed in Chapter 2.6. The population parameters are typical of a developing country, with low antenatal detection rates and poor adherence to scheduled outpatient visits.

The renal outcome in this study population is similar to reports from developed countries, with a calculated GFR < 60ml/min/1.73m2 at final visit in 37% of patients. The calculated GFR after relief of obstruction correlates well with the final calculated GFR. The presence of VURD or ascites offers no protection in renal outcome in this group of patients. Young age at presentation is associated with poor renal outcome. Type of surgery performed does not impact on renal outcome. However, the effect on bladder function needs to be assessed.

In this study, factors that correlate with poor somatic growth in boys with PUV include acidosis at final visit, young age at presentation, poor renal function, bilateral irregular uptake on DMSA scan, and initial and post surgery weight and height. There is no difference in final weight and height z- scores with primary valve ablation or vesicostomy.

South African children have additional disadvantages that limit optimal growth.

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Malnutrition is common with a low birth weight rate of 15% and stunting in 21% of children younger than 10 years old [58]. Infectious diseases, especially the human immunodeficiency virus (HIV) and tuberculosis (TB), are common causes of poor growth. These problems were not explored in this report.

5.1 Recommendations

- Antenatal detection rates need to improve. This may prove difficult in a resource-constrained setting, but the problem should be highlighted and early antenatal clinic visits encouraged to create the opportunity for antenatal screening.
- Parents need to be educated about the long term risk of renal deterioration to improve adherence to scheduled clinic visits.
- Contrary to National Institute of Health Clinical Excellence (NICE) guidelines [59], a sonar of the kidneys and bladder is recommended for every patient diagnosed with a UTI since antenatal detection rates are low. A VCU should be considered even if the abdominal sonar is normal.
- Small caliber resectoscopes should be made available since only one operation is necessary for primary valve ablation.
- Bladder function should be assessed and appropriately managed to prevent deterioration in renal function over time.
- Strict attention should be paid to UTI prophylaxis and treatment, correction of metabolic acidosis, and renal function in boys with PUV.
- All boys diagnosed with posterior urethral valves should be referred to specialist nephrology units for management and long term follow-up.

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APPENDIX A Ethics clearance certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Petersen

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M070206**
PROJECT	Outcome of Posterior Urethral Valves- Primary Ablation Versus Vesicostomy, A Twenty One Experience
INVESTIGATORS	Dr KL Petersen
DEPARTMENT	Department of Paediatrics
DATE CONSIDERED	07.03.02
DECISION OF THE COMMITTEE*	Approved subject to removing the hospital number and using codes. Written permission from the Hospital Superintendent must be submitted

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 07.03.05 **CHAIRPERSON** .....
(Professors PE Cleaton-Jones, A Dhai, M Vorster, C Feldman, A Woodiwiss)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Prof UK Kala

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX B **Data collection sheet**

Record number _____ Initials____ Date of birth_____

Year____

Age (months) at initial presentation _____

Age group 1 2 3 4

Antenatal diagnosis yes/ no

Features at presentation urinary tract infection yes/ no organism _____

obstruction yes/ no (dribbling, poor urinary stream)

abdominal distension

serum sodium decreased / normal / increased

other _____

date 1(presentation)	date 2 (6 months post surgery)	date 3 (final)
_____	_____	_____
weight 1(kg) _____	weight 2 _____	weight 3_____
z-score weight 1 __	z-score weight 2 ___	z-score weight3 ___
length 1 (cm) _____	length 2 _____	length 3 _____
z-score length 1 ___	z-score length 2____	z-score length 3 ___
creatinine 1 (umol/l) ___	creatinine 2 _____	creatinine 3 _____
GFR 1 _____	GFR 2 _____	GFR 3 _____
acidosis 1 yes/ no	acidosis 2 yes/ no	acidosis 3 yes/ no

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Ascites yes/ no

Hydronephrosis : none left right bilateral

VUR none left right bilateral Grade left_____ Grade right____

DMSA scarring none left right bilateral

Relative function left _____% right _____%

VURD yes/ no

Surgery primary valve ablation / vesicostomy Surgery date

Renal outcome CKD stage_____ Referred for renal transplant yes/ no

Duration of follow-up (months) _____ Lost to follow- up yes/ no

Death yes/ no date of death _____

WitsETD

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