TITLE PAGE

Title:

The effect of preoperative urinary tract infection on postoperative renal function in prenatally diagnosed ureteropelvic junction obstruction. Indications for the timing of pyeloplasty.

Running title:

Urinary tract infections and prenatally diagnosed ureteropelvic junction obstruction.

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ABSTRACT

Purpose: We reviewed renal function after pyeloplasty (PP) in cases of prenatally diagnosed ureteropelvic junction obstruction (PDUPJO) to determine the impact of preoperative urinary tract infection (UTI) on the timing of PP.

Methods: We retrospectively reviewed 81 cases of PDUPJO diagnosed between 1998 and 2013. Incidence of UTI was used to divide 37 kidneys requiring PP (3 bilateral) into U(-): UTI≤1; n=25 and U(+): UTI≥2; n=12 to compare age at PP, grade of hydronephrosis (HN) on ultrasonography (US), glomerular filtration rate (GFR) on diethylenetriaminepentacetic acid (DTPA) renography, and uptake on dimercaptosuccinic acid (DMSA) scintigraphy pre/post PP.

Results: Age at first UTI and age at PP were similar. HN improved significantly postPP in all cases. Although DTPA and DMSA were similar prePP, improvement postPP was better in U(-) than U(+), but only DMSA in U(-) was statistically significant (15.2 ±4.0% vs. 20±3.7%; p=0.049). There were no complications or UTI postPP.

Conclusion: Two or more UTI would appear to be associated with postPP renal dysfunction in PDUPJO. Thus, PP should be performed after the initial UTI, but before the second UTI.

Key words: hydronephrosis, ureteropelvic junction obstruction, prenatal diagnosis, urinary tract infection, renal function

INTRODUCTION

Improvements in routine fetal ultrasonography (US) have led to a marked increase in the diagnosis of a number of conditions including congenital hydronephrosis (HN). The most common cause of prenatally diagnosed HN is ureteropelvic junction obstruction (UPJO) [1-3]. However, the long-term clinical implications of prenatally diagnosed UPJO (PDUPJO) have hardly been reported.

At present, in most centers, management of PDUPJO involves observation with regular US or nuclear medicine studies, and pyeloplasty (PP) is reserved for patients with symptomatic obstruction or worsening renal function. However, early surgery is rarely recommended in the newborn and patients usually end up just having their renal function monitored while urinary tract infection (UTI) is treated as required. Therefore, it would be advantageous to have some prognostic clinical marker to assess preoperatively that is predictive of postoperative renal function and a marker of the timing for PP.

In this study, we defined UTI as fever (>38.0^{o}C) accompanied by leukocytosis with left shift and positive urine culture. Urinary stasis is a known risk factor for UTI [4], and UTI can cause renal scaring, which may contribute to complications such as hypertension or end stage renal disease. Thus, most pediatricians endeavor to prevent

UTI even though there are no established guidelines for the timing of PP based on history of UTI. The aim of this study was to determine if the incidence of preoperative UTI may affect postPP renal function in PDUPJO and whether it may be useful as an indicator for the timing of PP.

MATERIALS and METHODS

We reviewed the medical records of PDUPJO cases diagnosed at our institute between 1998 and 2013 (n=81). Of these, 37 kidneys in 34 cases (3 bilateral) requiring PP were the subjects for this study (Figure 1). These patients were divided into two groups according to incidence of UTI; U(-): 1 or less preoperative UTI (25 kidneys in 23 cases, male: female ratio=19:4), and U(+): 2 or more preoperative UTI (12 kidneys in 11 cases, male: female ratio=10:1).

Figure 1

We collected data for gestational age, birth weight, age and weight at the time of PP, HN grade on ultrasonography (US), radiologic findings (pre and postPP), glomerular filtration rate (GFR) on diethylenetriaminepentacetic acid (DTPA) renography, and uptake on dimercaptosuccinic acid (DMSA) scintigraphy. HN grade was scored according to the Society for Fetal Urology (SFU) grading system [5].

Routine US are performed at birth, and at 1, 3, and 6 months old then 6

monthly. If HN is SFU grade≥ 3 or after a UTI, DTPA and DMSA are performed approximately once every 6 to 12 months, however, after a UTI, DMSA is postponed for an interval of 3 months to exclude any effect of acute inflammation on uptake.

At birth all PDUPJO were commenced on prophylactic antibiotics and reviewed according to clinical status. Percutaneous nephrostomy was indicated if HN was SFU grade> 3 with acute signs of deterioration due to compression, such as vomiting, dyspnea, or abdominal distension. Prophylactic antibiotics were continued after UTI and commenced after nephrostomy as required. Surgical intervention in both groups was indicated if there was no improvement in SFU grade over 2-3 years, persistence of urinary obstruction on DTPA, declining GFR, declining uptake on DMSA, or split renal function of less than 40%. Our preferred technique for PP is the Anderson-Hynes dismembered PP with ureteric stents at the time of surgery and all cases were treated under the supervision of one board-certified specialist pediatric surgeon (AY) with extensive experience. Postoperative DMSA and DTPA were evaluated at least one year after PP.

Data were expressed as mean ± standard deviation or median value. The Student's *t*-test, Mann-Whitney U test, and Chi-squared test were used for statistical analysis. A p value < .05 was considered to be statistically significant. This study

was approved by the Juntendo University School of Medicine Institutional Review Board and complies with the Helsinki Declaration of 1975 (revised 1983).

RESULTS

All PP were successful without any complications. There were no significant differences in age and body weight at PP between the two groups (1.7±1.1 years vs. 2.2±1.5 years; 9.7±2.7kg vs. 10.7±3.1kg; U(-) vs. U(+), respectively) (Table1). Table 1

Demographic data are summarized in Table 2. There were no significant differences between the two groups, although there were 2 major cardiac associated anomalies in U(-). Nephrostomies were present in 13/37 kidneys (35%); 7/25 in U(-) (28%) and 6/12 in U(+) (50%) (*p*=NS). There were 17 kidneys in U(-) (68%) with no history of UTI. Mean age at first UTI was similar for both groups (4.0±3.1 months vs. 3.8±3.3 months; *p*=NS). Mean age at second UTI in U(+) was 8.8±3.6 months (n=12 kidneys), third UTI was 24.8±0.7 months (n=4 kidneys) and fourth UTI was 44 months (n=1 kidney). Table 2

Median SFU HN grades were similar for U(-) and U(+) prePP and there was significant improvement in HN grades postPP in both groups; for U(-), prePP vs. postPP was 3 vs. 1 and for U(+), prePP vs. postPP was 3 vs. 2, $p < .01$, respectively. See

Figure 1

Tables 3,4. While there were no significant differences for GFR on DTPA between the 2 groups (49.2±16.9mL/min vs. 41.6±7.4mL/min; U(-) vs. U(+); *p*=NS), mean postPP GFR on DTPA in U(-) was significantly increased compared with U(+) (56.4±13.6mL/min vs. 41.4±11.2mL/min; U(-) vs. U(+); $p < .05$) (Figure 1) and prePP GFR on DTPA ($p < .05$). There was a similar pattern observed for uptake on DMSA. PrePP uptake on DMSA was not significantly different between the two groups, (15.2±4.0% vs. 15.2±5.1%; U(-) vs. U(+); *p*=NS), mean postPP uptake on DMSA was significantly increased in U(-) compared with U(+); (20.0±3.7% vs. 14.7±3.8%; $p < .05$) (Figure 2) and prePP uptake on DMSA ($p < .05$).

Table 3

Table 4

There were no significant differences in duration of follow-up between the 2 groups (5.0±1.7 years vs. 6.2±2.5 years; U(-) vs. U(+); *p*=NS).

DISCUSSION

To the best of our knowledge, our study is the first to investigate the correlation between preoperative UTI and postoperative renal dysfunction in PDUPJO. In our study, SFU grade of HN at birth was similar in both groups and because all our subjects were diagnosed and managed identically prior to PP, we believe any differences in

outcome can be attributed to the incidence of UTI, which to date has not generally been regarded as a prognostic factor in PDUPJO. This is a major distinction between our study and other reports in the literature [6,7] that also include PDUPJO cases who did not undergo PP.

For our patients with PDUPJO, we perform routine studies to assess renal function during follow-up. Should patients become symptomatic, develop UTI, or demonstrate a significant loss of renal function on nuclear scanning, we actively consider them for surgical intervention. Some investigators have reported that with surgery, including PP, renal function is expected to recover to baseline values. Chertin et al reviewed 44 patients who were managed conservatively but underwent surgery specifically because of functional deterioration. Ninety-five percent had recovery of function to baseline values [8]. Chandrasekharam et al reported that functional improvement may take up to 1 year after surgery if it occurs [9]. Our results support these findings as shown in Figures 2 and 3 where both GFR on DTPA and uptake on DMSA recovered post-PP more in U(-) than U(+) in spite of equivalent improvement in SFU grade of HN postPP in both groups. There may be some influence of growth and development on renal function in children, but in this study, both groups were similar for age and weight which would further indicate that the number of UTI affects postPP

renal function directly in PDUPJO.

Antibiotic prophylaxis has been advocated because UTI are universally regarded as having the potential to be deleterious to renal function. However, there are no data available suggesting that antibiotic prophylaxis is associated with better outcome in PDUPJO. Madden et al [10] formally evaluated the use of antibiotic prophylaxis in their patient population. Although their study was retrospective, they found no statistically significant difference in the rate of UTI in patients with UPJO receiving antibiotic prophylaxis compared with those not receiving antibiotic prophylaxis. On the other hand, Song et al [11] reported there was a much higher incidence of UTI in infants with severe obstructive HN of the upper urinary tract and recommended that infants with severe HN (SFU grade 3 or 4) due to obstruction of the upper urinary tract should be treated with prophylactic antibiotics.

A number of factors have been described in PDUPJO that may influence the incidence of UTI [6]. Female gender is generally regarded by many investigators as an independent risk factor for UTI, and the incidence of UTI is roughly 10 times greater in girls with urologic pathology than boys with no urologic pathology. However, our data did not indicate any female preponderance in the incidence of UTI. Interestingly, all UTI in U(+) developed while on prophylactic antibiotics which theoretically should

prevent UTI and some cases developed UTI while others did not, but the mean age at first UTI is comparable to other reports in the literature [11, 12]. Compliance could be implicated but is beyond the scope of this study. Obviously antibiotic prophylaxis is only effective if compliance is good and compliance may not have been good in our U(+) subjects. Our results would suggest that long-term antibiotic prophylaxis does not fully prevent UTI in PDUPJO.

In summary, improvement in renal function postPP may be predicted by the incidence of prePP UTI, specifically, the absence of recurrent UTI. In other words, 2 or more UTI would appear to be a factor associated with postoperative renal dysfunction in PDUPJO. Thus, PP should be performed after the first UTI but before the second to best prevent postoperative renal dysfunction.

FIGURE LEGENDS

Figure 1: Comparison of GFR.
There were significant differences in GFR postPP between both groups (*p< .05), but no differences identified prePP (p=NS).
GFR: glomerular filtration rate
PP: pyeloplasty

NS: not significant

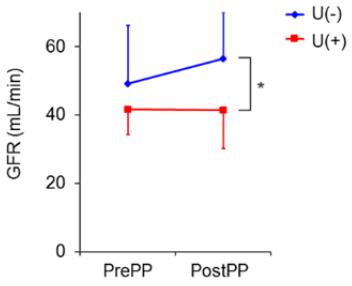

Figure 2: Comparison of uptake on DMSA scintigraphy.

There were significant differences in uptake postPP between both groups (*p< .05), but no differences identified prePP (p=NS). Uptake improved significantly only in U(-) ($^{\#}p$< .05).

DMSA: dimercaptosuccinic acid

PP: pyeloplasty

NS: not significant

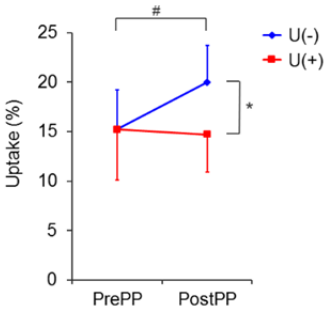

Table 1 Age/weight at the time of PP

	U(-) (n=25 kidneys)	*U(+) (n=12 kidneys)*	*P*
Age at PP (years)	1.7 ± 1.1	2.2 ± 1.5	NS
Weight at PP (kg)	9.7 ± 2.7	10.7 ± 3.1	NS

PP: pyeloplasty

NS: not significant

Table 2 Demographic data

	U(-) (n=25 kidneys)	*U(+) (n=12 kidneys)*	*P*
Gestational age (weeks)	38.6 ± 1.4	38.7 ± 1.6	NS
Birth weight (kg)	3.1 ± 0.2	2.9 ± 0.5	NS
SFU grade at birth	3.4 ± 0.6	3.7 ± 0.5	NS
Concurrent anomalies (%)	8.0	0	NS
Nephrostomy prePP (%)	28	50	NS

SFU: Society for Fetal Urology

PP: pyeloplasty

NS: not significant

Table 3 Comparison of SFU grades for HN in U(-)

SFU grades	0	1	2	3	4
prePP (kidneys)	0	2	2	11	10
postPP (kidneys)	4	13	7	1	0

SFU: Society for Fetal Urology

HN: hydronephrosis

PP: pyeloplasty

NS: not significant

There was significant improvement in median SFU grade prePP vs. postPP in U(-): 3 vs. 1. ($p < .01$)

Table 4 Comparison of SFU grades for HN in U(+)

SFU grades	0	1	2	3	4
prePP (kidneys)	0	0	3	7	2
postPP (kidneys)	1	4	5	2	0

SFU: Society for Fetal Urology

HN: hydronephrosis

PP: pyeloplasty

NS: not significant

There was significant improvement in median SFU grade prePP vs. postPP in U(+): 3 vs. 2; ($p < .01$)

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