Fetal Surgery for Posterior Urethral Valves: Long-Term Postnatal Outcomes

Nicholas Holmes, MD*; Michael R. Harrison, MD‡; and Laurence S. Baskin, MD*

ABSTRACT. Objective. Fetal surgery for obstructive uropathy was first performed at the University of California, San Francisco in 1981. Indications for treatment were bilateral hydronephrosis with oligohydramnios. Preintervention criteria included fetal urinary electrolytes with β-microglobulin levels, karyotyping, and detailed sonography specifically looking for renal cortical cysts. We reviewed the outcomes of children who underwent fetal intervention with specific long-term follow-up in patients who were found postnatally to have posterior urethral valves.

Methods. A retrospective review of the University of California, San Francisco fetal surgery database was performed for patients with a prenatal diagnosis of obstructive uropathy. Medical records from 1981 to 1999 were reviewed. Long-term follow-up was documented if the cause of the urinary tract obstruction was posterior urethral valves. We collected data points, focusing on time and type of intervention, fetal urinary electrolytes, appearance of fetal kidneys, present renal function, length of follow-up, and present status of the urinary tract.

Results. Forty patients were evaluated for fetal intervention; 36 fetuses underwent surgery during this time period. Postnatal confirmation of posterior urethral valves was demonstrated in 14 patients. All patients had favorable fetal urinary electrolytes. Mean gestational age at intervention was 22.5 weeks. The procedures performed included creation of cutaneous ureterostomies in 1, fetal bladder marsupialization in 2, in utero ablation of valves in 2, and placement of vesicoamniotic catheter in 9. Six deaths occurred before term delivery with premature labor and the newborns succumbing to respiratory failure. One pregnancy was terminated electively because of shunt failure and declining appearance of fetal lungs and kidney. The remaining 8 living patients had a mean follow-up of 11.6 years. Chronic renal disease with abnormal serum creatinine was present in 5 patients. Two patients have undergone renal transplantation, and 1 is awaiting organ donation. Five of the 8 living patients have had urinary diversion with vesicostomy, cutaneous ureterostomy, or augmentation cystoplasty with later reconstruction.

Conclusions. Fetal intervention for posterior urethral valves carries a considerable risk to the fetus with fetal mortality rate of 43%. The long-term outcomes indicate that intervention may not change the prognosis of renal function or be a predictor for possible urinary diversion. Despite all of these patients' having favorable urinary electrolytes, this did not seem to have any implication postnatally. When counseling families about fetal intervention, efforts should be focused on that intervention may assist in delivering the fetus to term and that the sequelae of posterior urethral valves may not be preventable. Fetal surgery for obstructive uropathy should be performed only for the carefully selected patient who has severe oligohydramnios and "normal"-appearing kidneys. Pediatrics 2001;108(1). URL: http://www.pediatrics.org/cgi/content/full/108/1/e7; fetal surgery, obstructive uropathy, valves, urethral valves.

Fig 1. Cytoscopic evaluation of posterior urethral valves before treatment (black arrows outlining valves).
occurring in between 1 in 8000 to 1 in 25,000 live births.\textsuperscript{1} Posterior urethral valves affect both the upper and the lower urinary tract, causing abnormalities of renal dysplasia (Fig 2), as well as changes in tubular function. Posterior urethral valves also are associated with vesicoureteral reflux (Fig 3), as well as changes in bladder function (Fig 4). In a large retrospective series from the Children’s Hospital of Philadelphia comprising 100 patients who were treated in the newborn period, one-third eventually went on to have chronic renal failure.\textsuperscript{2} This retrospective series reviewed the 10- to 20-year follow-up (mean: 11.2 years) and stratified the patients who were treated by primary valve resection (74%), vesicostomy (13%), and high urinary diversion (9%). Critical outcome analysis of the different treatments showed no statistical difference in the incidence of chronic renal disease.

Historically poor renal outcomes even with aggressive postnatal relief of obstruction have inspired attempts to relieve urinary obstruction during fetal development. Potential candidates for fetal surgery have been considered for intervention if prenatal ultrasound depicts significant bilateral hydronephrosis with oligohydramnios. These sonography criteria are consistent with a diagnosis of bladder outlet obstruction secondary to posterior urethral valves. However, postnatal evaluation has confirmed the lack of prenatal sonographic specificity with a number of patients who had prune belly syndrome, uretero-pelvic junction obstruction, urethral atresia, and urogenital sinus anomalies. Prognostic criteria were developed on the basis of fetal urinary electrolytes (sodium, chloride, and osmolarity) in an attempt to maximize therapy and preserve renal function. Fetal sonography was refined further to note associated structural anomalies, signs of renal dysplasia (cortical cysts and increased echogenicity), and location and character of the placenta. In addition, fetal karyotyping, with either amniocentesis or fetal blood sampling, was performed to exclude chromosomal abnormalities.

Herein, we review the long-term outcomes of children who underwent fetal intervention and were confirmed postnatally to have had obstructive uropathy secondary to posterior urethral valves. We specifically excluded patients who were found postnatally to have other diagnoses, such as prune belly syndrome and uretero-pelvic junction obstruction, because the pathophysiology of the prenatal hydronephrosis and the postnatal outcome of the dilated urinary tract are different in these cases. The long-term outcome was compared with the natural history of untreated posterior urethral valves in attempt to compare whether prenatal intervention had a positive effect on patient outcome.

METHODS

A retrospective review of the University of California, San Francisco fetal surgery database from 1981 to 1999 was performed for all patients with a prenatal diagnosis of obstructive uropathy (defined as bilateral hydroureteronephrosis, an enlarged bladder with dilated posterior urethra, and oligohydramnios). Patients were selected for more detailed review if fetal procedures had been undertaken to treat the obstructive uropathy. Long-term follow-up was documented if the cause of urinary tract obstruction was confirmed postnatally to be posterior urethral valves. Data points that focused on the following were collected:

1. Time/type of intervention
2. Fetal urinary electrolytes
3. Fetal renal ultrasonographic appearance (e.g., cortical cysts, echogenicity)
4. Postnatal renal function
5. Postnatal status of the urinary tract

RESULTS

Forty patients were evaluated for fetal intervention; 36 fetuses underwent surgery during this period for presumed obstructive uropathy. The most recent intervention for obstructive uropathy was performed in October 1999 with laser ablation of valves via fetal endoscopy. Postnatal confirmation of posterior urethral valves was demonstrated in 39\% (14 of 36) of the fetuses who had prenatal intervention. The remaining 22 patients had diagnoses of prune belly syndrome, uretero-pelvic junction obstruction, urogenital sinus anomalies, or urethral atresia (Table 1). All valve patients had favorable fetal urinary electrolytes with a sodium concentration <100 mEq/L, chloride concentration <90 mEq/L, and osmolarity level <210 mOsm (Table 2). Serial urinary electro-

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Fig 2. Findings of renal dysplasia on prenatal ultrasound of fetus with posterior urethral valves. A) Transverse views of kidney with severe hydronephrosis, parenchymal thinning, and increased echogenicity of parenchyma. B) Sagittal view of upper pole of kidney with renal cyst.
lytes were obtained via ultrasound-guided percutaneous fetal bladder aspiration. The initial bladder aspiration was thought to be representative of stagnant, old urine, and subsequent serial measurements were used to determine true renal function. When these urinary electrolytes trended toward “normal” values, they were considered favorable. Mean gestational age at intervention was 22.5 weeks (range: 18-28 wk).

**TABLE 1.** Confirmed Postnatal Diagnosis Treated by Fetal Intervention

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of Patients (N = 40)</th>
</tr>
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<tbody>
<tr>
<td>Prune belly syndrome</td>
<td>19</td>
</tr>
<tr>
<td>Posterior urethral valves</td>
<td>14</td>
</tr>
<tr>
<td>Uretero-pelvic junction obstruction</td>
<td>4</td>
</tr>
<tr>
<td>(unilateral)</td>
<td></td>
</tr>
<tr>
<td>Urogenital sinus anomalies</td>
<td>2</td>
</tr>
<tr>
<td>Urethral atresia (female)</td>
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**TABLE 2.** Fetal Urinary Electrolytes

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Gestational Age</th>
<th>Sodium (mEq/L)</th>
<th>Chloride (mEq/L)</th>
<th>Osmolarity (mOsm)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>20 wk</td>
<td>98</td>
<td>84</td>
<td>210</td>
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<tr>
<td>2</td>
<td>18 wk</td>
<td>95</td>
<td>82</td>
<td>205</td>
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<td>3</td>
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<tr>
<td>14</td>
<td>30 wk</td>
<td>70</td>
<td>68</td>
<td>158</td>
</tr>
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</table>

All values listed represent last set of electrolytes in serial bladder aspirations. Bold indicates living patients.
Renal sonographic abnormalities associated with renal dysfunction were identified in 2 patients. One patient had both increased echogenicity, as compared with liver parenchyma, and renal cortical cysts, and the other patient solely had increased echogenicity of the renal parenchyma.

The procedures performed included creation of cutaneous ureterostomies in 1, fetal bladder marsupialization in 2, in utero antegrade, laser ablation of valves in 2 (using fetal endoscope), and placement of vesicoamniotic catheter in 9 (Table 3). One patient required vesicoamniotic shunt placement after in utero ablation of valves as a result of rising abdominal ascites. Another required multiple shunt placements as a result of malfunction of the primary catheter and migration of the others.

Six deaths occurred before term delivery, representing a fetal mortality rate of 43% (6 of 14). One pregnancy was terminated electively as a result of shunt failure and declining appearance of fetal lungs on ultrasound (signs of progressive pulmonary hypoplasia, eg, increase echogenicity, decrease parenchymal volume). The remaining deaths were a result of premature labor precipitated by chorioamnionitis, spontaneous ruptures of membrane, or amniotic fluid leak. This occurred anywhere from 72 hours to 16 weeks postintervention (Table 3). All premature delivery deaths were the direct result of respiratory failure soon after birth. The remaining 8 living fetuses had a mean follow-up of 11.6 years (range: 12 months to 19 years).

Chronic renal disease with abnormal serum creatinine occurred in 5 (63%) of 8 of the living patients. Mean serum creatinine after 1 year of age was 2.5 mg/dL (range: 1.3–3.3 mg/dL). Two of the 5 patients have undergone renal transplantation. One of the 5 patients with renal failure is awaiting renal transplantation as a result of worsening acidosis, growth retardation, and severe anemia unresponsive to medical interventions.

Five (63%) of the 8 living patients have had urinary diversion with vesicostomy, cutaneous ureterostomy, and/or augmentation cystoplasty. Urinary diversion was performed as a result of rising serum creatinine, worsening hydronephrosis, and/or recurrent urosepsis secondary to poor urinary drainage. Initial urinary diversion was with a vesicostomy in 3 patients and cutaneous ureterostomy in 2. All patients have undergone urinary reconstruction of the previous diversion, and 1 patient has required an augmentation cystoplasty.

Urodynamic evaluation of the valve bladder was performed in 3 of the 8 living patients (Table 4). One patient had multiple urodynamic evaluations as a result of recurrent episodes of pyelonephritis and urinary incontinence. Normal bladder compliance (Δvolume/Δpressure) was exhibited in all 3 patients. Uninhibited bladder contractions were seen in all of the patients. Total bladder capacity was decreased only in the patient who had a vesicostomy. No vesicoureteral reflux was demonstrated in any of these patients. Decreased ability to empty the bladder, noted as high postvoid residuals, was demonstrated in 2 of the 3 patients.

**DISCUSSION**

With the advent of prenatal ultrasound, theoretically the diagnosis of posterior urethral valves can be made early in gestation. Early diagnosis can prompt fetal treatment to relieve the obstructive uropathy, thereby restoring amniotic fluid levels and allowing normal pulmonary maturation. Whether early intervention for obstructive uropathy may prevent progressive renal deterioration or improve long-term renal outcomes remains to be determined.

Fetal surgery for various congenital anomalies represents a significant technical advance in medicine. Areas in which intervention has made an impact on postnatal outcomes include treatment of congenital diaphragmatic hernias, correction of twin-twin transfusion syndrome, and treatment of pulmonary lesions such as congenital cystic adenomatoid malformation. Particular management in utero of spina bifida, hydrocephalus, and obstructive uropathy continues to remain highly controversial. Can open surgery or minimally invasive procedures with percutaneous shunt placements and fetoscopy relieving...
whether the kidney is worth saving. The presence of increase in renal echogenicity can truly determine in revealing the presence of cortical cysts or an not noted. Others suggest that ultrasound’s sophisticated in the human fetus when these critical findings are come. Thus irreparable damage may have occurred or before 24 weeks predicted poor outcome. Even though a normal-appearing kidney does not rule out significant disease.

Fetal ultrasonography indirectly gives information on the potential renal function, but the true accuracy of predicting obstruction, a dynamic process, has been questioned. One study suggested that ultrasound is not the proper study with which to make this diagnosis. Approximately 34% of the cases did not exhibit postnatally the findings of bladder outlet obstruction as seen on prenatal ultrasound. In addition, other studies suggest that postnatal outcomes are not truly different in those who did not have an in utero diagnosis of valves. Screening obstetric ultrasound series have determined that the incidence of hydronephrosis varies from 0.48% to 1.4%, Findings of bilateral hydroureteronephrosis, a dilated bladder with a “keyhole” sign (dilated posterior urethra), and oligohydramnios tend to suggest the presence of bladder outlet obstruction. These findings have been noted to have a positive predictive value of 34.6% in a large series of prenatal ultrasounds. This finding was demonstrated in all of the patients in the present series. The skill level of the obstetric ultrasonographer, the ability of the obstetric ultrasonographer to delineate the normal from the abnormal, and the time of gestation have a profound impact on the correct diagnosis. Potentially, other radiologic modalities, eg, fetal magnetic resonance imaging, may assist in accurately defining obstructing anatomic lesions of the posterior urethra from functional causes of severe hydronephrosis, eg, prune belly syndrome and vesicoureteral reflux. To date, however, fetal magnetic resonance imaging has not been able to distinguish posterior urethral valves from prune belly syndrome (A. Hubbard, Department of Radiology, Children’s Hospital of Philadelphia, personal communication, 1999).

Fetal urinary electrolytes as a prognostic factor have been debated widely. The normal fetal kidney makes hypotonic urine as the placenta handles the majority of excretory and homeostatic function of the fetus. Studies by Glick et al suggest that a fetal

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Age (Year)</th>
<th>Capacity (mL)</th>
<th>Storage Pressure (cm H₂O)</th>
<th>Postvoid Res (mL)</th>
<th>Reflux Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>7</td>
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<td>25</td>
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<td>12</td>
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<td>20</td>
<td>125</td>
<td>No</td>
</tr>
<tr>
<td>4*</td>
<td>1</td>
<td>49</td>
<td>30</td>
<td>0</td>
<td>No</td>
</tr>
</tbody>
</table>

* Had vesicostomy.
urinary sodium <100 mEq/L and β-2 microglobulin are the best predictors of renal function. In series by Wilkins et al and Elders et al, each described fetuses with discordance between the urinary electrolytes and postnatal renal dysplasia in 50% of the cases. Others suggest that the use of fetal urinary biochemical markers before 20 weeks’ gestation has discordance with pathologic examination of renal tissue in terms of the presence of dysplasia. Having β-2 microglobulin fetal serum levels seems to be a more appropriate predictor of postnatal serum creatinine in the fetus with obstructive uropathy in addition to fetal urinary levels. Although all of the patients in the present series had favorable urinary electrolytes, 63% (5 of 8) of the living patients had chronic renal failure. This suggests that the reliability of fetal urinary electrolytes, at least in a patient with posterior urethral valves, should not be the sole criteria for intervening on what seems to be the “normal” or salvageable kidney.

Fetal intervention for obstructive uropathy secondary to posterior urethral valves, whether open surgical or minimally invasive procedures, has yet to secure survival of the unborn patient. One must take into consideration that the majority of these procedures were performed early in the fetal surgery experience. With each case, efforts were made to reduce maternal/fetal morbidity. Tocolytic regimens, perioperative antibiotics, and steroids for fetal lung maturity have decreased some of the morbidity resulting from fetal surgery. Premature labor seems to occur in close to 100% of the fetal cases for various disease processes despite tocolytic regimens. Our series of valve patients had a fetal mortality rate of 43%. In comparing other series, fetuses who had the diagnosis of valves and who underwent intervention had a fetal mortality rate of 33%. The significant difference between these 2 groups may be because the other series solely had vesicoamniotic shunting performed. In addition, a selection bias or referral bias may be present because the University of California, San Francisco at one time was the sole center for fetal surgery. Mean gestational age in review of this series was not noted, but a later analysis of all patients with the presumptive diagnosis of obstructive uropathy shunting was performed at 22 weeks with a mortality rate of 38%. Most centers that use vesicoamniotic shunting reserve it for the fetus who is diagnosed late in gestation as a result of problems with catheter migration, malfunction, and infection. A fetus that undergoes intervention later in gestation may have been detected later and thus have an overall good prognosis. Bladder function as a result of fetal intervention may be more difficult to assess. The valve bladder syndrome, as noted by Mitchell, is characterized as a thick-walled, poorly compliant bladder that stores urine at high pressures. Initially, it was thought that this was a direct result of defunctionalization of the bladder with urinary diversion (e.g., vesicostomy, cutaneous ureterostomy). The valve bladder probably is a result of the degree of the initial obstruction causing secondary changes to the bladder, e.g., detrusor muscle hypertrophy, increase deposition of connective tissue, and changes in types of collagen to less-pliable forms. The urodynamic parameters of valve patients are known to change as the patient ages. This is irrespective of the primary treatment, whether valve ablation or urinary diversion. The small number of patients in our series had similar findings to historical series of valve patients despite having had in utero relief of urethral obstruction.

End-stage renal disease secondary to posterior urethral valves has a wide range of occurrence in the prenatally diagnosed boy. Renal failure has been estimated to occur in 19% to 64% of males who are diagnosed prenatally and in 25% to 40% of valve patients who are diagnosed postnatally. Of the patients that develop renal failure, approximately one third do so after birth and the remainder during the late teenage years. We hypothesize that the infants who develop renal failure after birth are born with severe dysplasia and do not have enough renal tissue to survive without dialysis. Renal disease that develops later in life may be secondary to increasing metabolic demands of somatic growth, overloading poor renal reserve, or renal blood flow hyperfiltration. In those who undergo fetal intervention, renal failure has been exhibited in 33% of valve patients. In stark contrast, 63% (5 of 8) of our series had renal failure postnatally, and 2 have undergone renal transplantation. This suggests that any type of prenatal intervention did not reverse the outcome of renal dysfunction. The fate of the kidneys may already be decided by the time of any intervention. However, 3 of 8 surviving patients have normal renal function, which may not have been the case without intervention, although normal outcomes certainly can occur without intervention. The small number of patients and the variability of presentation and severity of posterior urethral valves make prospective prenatal trials difficult.

CONCLUSION

Fetal intervention for posterior urethral valves carries a considerable risk to the fetus, with a fetal mortality rate of 43%. The long-term outcomes indicate that intervention does not seem to change the prognosis of renal function despite the presence of favorable ultrasound findings and urinary electrolytes. Although favorable urinary electrolytes were present, this did not seem to have any implication postnatally. The history of fetal surgery has improved in terms of the morbidity experienced by the mother and the fetus. Fetal surgery, (vesicoamniotic shunting and endoscopic techniques) for posterior urethral valves is performed only for the carefully selected patient who has normal-appearing kidneys and normal urinary electrolytes with severe oligohydramnios. When counseling families about fetal intervention, efforts should be focused on that intervention could assist in delivering the fetus to term. The renal sequelae of posterior urethral valves may not be prevented by our various procedures. We must not give families unrealistic expectations that fetal surgery is the cure for obstructive uropathy or that the child will not need extensive follow-up after delivery.
Although the present study does not support the use of prenatal intervention for the preservation of renal function in patients with posterior urethral valves, with technological advances in minimally invasive surgery and improved tocolytic agents, it may be possible for optimism in the future. Although renal function may be predetermined, prenatal treatment to improve bladder function, thus decreasing the morbidity of incontinence and infection, may be possible. We strongly advocate that future efforts to care for the unborn child with obstructive uropathy be performed only at centers with extensive experience and in a controlled manner.

REFERENCES

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