Fetal Uropathy: Lessons Learned

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As Herbert Eckstein's senior registrar at Great Ormond Street, I was fortunate in being given the opportunity to review 117 children with hydronephrosis treated by him between 1964 and 1979. In those days children presented typically with pain or infection and the diagnosis of PUJ obstruction was made by intravenous urography. However, by the time the paper based on this work [29] found its way into print, the first few case reports of the prenatal detection of urinary tract anomalies were already heralding a new era in pediatric urology. During the 1980s the widescale introduction of high resolution ultrasound into obstetric practice has had a major impact on pediatric surgery and pediatric urology in particular.

In contrast to the children whose urinary tract malformations presented to Herbert Eckstein with signs and symptoms, infants with prenatally detected uropathies are mainly asymptomatic and outwardly normal at birth. Ultrasound imaging of the fetus has become an established part of obstetric practice and the task now facing pediatric surgeons and urologists is to define situations in which the information derived from prenatal ultrasound can be translated into practical benefit for affected infants. Coupled with this aim is the need to minimise invasive investigation in healthy infants and to avoid unnecessary parental anxiety.

Incidence of prenatally detected uropathy

The frequency with which congenital abnormalities of the urinary tract are identified on prenatal ultrasound is governed by two factors:

1. The gestational age at which obstetric ultrasound scanning is routinely performed.
2. The definition of "abnormality", i.e. the point at which dilatation acquires pathological significance.

In the United Kingdom virtually every pregnant woman is scanned at least once in pregnancy, usually around 17 to 19 weeks of gestation when the legal timescale still permits parental counseling and possible termination of pregnancy. Although ultrasound imaging at 17 to 19 weeks is sufficiently sensitive to detect the majority of lethal congenital anomalies, large numbers of anomalies at the non-lethal end of the spectrum are not associated with detectable dilatation at this gestational age. In a prospective study reported by Helin and Persson [15], 11,986 pregnancies were scanned at 17 and 33 weeks. In total 33 urinary tract anomalies were identified, but only three (9%) were evident on the 17 week scan whilst in the remaining 30 cases, the fetal uropathy was not evident until the second scan at 33 weeks. We recently studied [3] the possible correlation between second trimester ultrasound appearances and functional outcome in 35 cases of prenatally detected PUJ obstruction. In 11 cases (31%), however, the fetal kidneys had appeared entirely normal during the second trimester and it was only because ultrasound had been performed in later pregnancy that these cases came to light. Surprisingly it has emerged that even in cases of posterior urethral valves, the most severe form of non-lethal obstructive uropathy, the ultrasound appearances in the second trimester may be entirely normal.

Dinneen et al [8] reviewing 19 cases of prenatally detected posterior urethral valves at Great Ormond Street noted that second trimester ultrasound had failed to detect 16 (84%). In our experience [16] of 31 prenatally detected cases of posterior urethral valves, the detection rate during the second trimester ultrasound was higher but nevertheless 14 (45%) of the prenatally detected cases had non dilated urinary tracts in the second trimester.

What constitutes a fetal urinary tract "abnormality"?

Some anomalies, for example multicystic dysplastic kidney, duplication, severe hydronephrosis, are immediately evident on ultrasound but in many instances the reported "abnormality" consists of mild or moderate dilatation confined to the renal pelvis or pelvis and calices. In an on-going study designed to establish the incidence, natural history and clinical significance of mild dilatation of the fetal renal pelvis, Chitty et al [5] have reported an incidence of 0.62 per 100 deliveries (a total of 84 in 13,500 deliveres), Rosendahl [24], defining abnormality as an antero-posterior diameter of the renal pelvis of 1 cm or more, reported an incidence of abnormal findings in 0.48% of fetuses, i.e. 1: 208. In Leeds routine second trimester ultrasound combined with later ultrasound performed on a non-systematic basis for obstetric indications identified significant urinary tract anomalies in 78 out of 46,775 fetuses, i.e. an incidence of 1: 600 [2].

In summary, our own data and those from other European centres suggest that the overall incidence of detectable dilatation is currently of the order of 1:100 pregnancies whilst the incidence of significant uropathies for which postnatal surgery or termination of pregnancy may be considered is of the order of 1:500. We can reasonably anticipate that the increasing use of third trimester ultrasound will be reflected in a higher detection rate of non lethal uropathies.

Fetal surgery

The scientific rationale for intrauterine drainage procedures has its origins in the impressive research programme mounted by Harrison [14] and his colleagues in San Francisco in the 1980s. Having created urethral obstruction in the fetal lamb, Harrison's group then demonstrated that intrauterine drainage prevented pulmonary hypoplasia and renal dysplasia in this experimental model. Undeterred by the lethal outcome of Harrison's first reported case of fetal surgery in man, obstetricians in centres across the world embarked on fetal surgery on a largely uncontrolled basis. The reported results have been uniformly disappointing. The Fetal Surgery Registry [20] reported an overall mortality rate of 59% in 73 cases and a review of a further 57 cases by Elder et al [10] highlighted a 45% incidence of significant complications including premature labour in 12%. Enthusiasm for fetal intervention is waning. Reviewing the literature on fetal intervention at the close of the 1980s, Mandell et al [19] identified 24 publications on fetal intervention between 1982-85 but only 7 between 1985-89, 2 of which had a cautionary message and 2 consisted of single case reports.

A number of anatomical and biochemical predictors of outcome have been studied in the hope of identifying the small group of fetuses who might benefit from treatment whilst selecting out those with irreversible pulmonary and renal damage. These predictors include:

1. Severe oligohydramnios.

2. Ultrasound appearances of renal dysplasia, i.e. "bright" echogenic cortex and the presence of small cortical cysts.

3. Fetal urinary biochemical markers. Biochemical analysis of samples of fetal urine obtained by suprapubic aspiration has revealed a correlation between some markers of tubular function and subsequent outcome. Harrison's group [7] has concluded that fetal urinary sodium of <100 mol/litre, chloride <90 mol/litre and osmolarity >210 osmls/per litre are predictors of likely survival. In addition, Mandelbrot et al [18] have reported that the level of β_2 microglobulin in the fetal urine is also a useful predictor of postnatal renal function.

Techniques employed to drain the fetal urinary tract in utero have included:

1. Vesico amniotic shunting, i.e. ultrasound guided percutaneous placement of a pigtail stent into the fetal bladder.

2. Hysterotomy and open surgery. Eight cases of open fetal surgery have been reported by the San Francisco [9] group.

3. Fetoscopy and the placement, under vision, of a purpose designed expandable wire mesh suprapubic stent. This technique is currently being tested in primates prior to possible use in man [9].

There is some essentially anecdotal evidence to indicate that fetal intervention may prevent death from pulmonary hypoplasia in some instances. Unfortunately severe degress of renal dyplasia appear

to be less amenable to fetal intervention and survivors are often destined for chronic renal failure, dialysis and transplantation in childhood.

In the author's view, it is difficult to defend the use of fetal intervention outside the few centres in the world where the technique is being researched on a scientifically rigorous basis.

Postnatal diagnosis and management of fetal uropathy

The guiding aims of diagnosis and management can be summarised as:

1. Preserving renal function.
2. Preventing morbidity, notably urinary infection.
3. Minimising invasive intervention and parental anxiety.

Investigations usually begin with a postnatal ultrasound scan. Ideally this should be deferred until around 24/48 hours of age when a representative fluid intake and urine output have been established. The ultrasound findings on this initial postnatal scan then guide the pattern of further investigation. Anomalies which have a distinctive ultrasound appearance such as the multicystic dysplastic kidney or renal duplication are studied by a standardised sequence of tests. Frequently, however, ultrasound reveals dilatation of the pelvis alone or pelvis and calices. In this situation the first question to ask is whether the dilatation is sufficiently severe to merit any further investigation other than a follow up ultrasound scan.

In the absence of ureteric dilatation or a dilated, thick-walled bladder, we no longer believe it appropriate to subject infants to the distress and radiation dosage of a voiding cystogram. Similarly, isotope renography is limited to those cases in which the AP diameter of the renal pelvis exceeds 1.5 cm.

Mild dilatation (pyelo-caliectasis)

Possible explanations for this common ultrasound finding include "flow uropathy" (at term the normal fetus has a urine output which is four times greater than the output in early postnatal life), low grade or self-limiting PUJ obstruction and vesicoureteric reflux. Alternatively the finding may simply represent a prominent extrarenal pelvis. To assess the postnatal morbidity of prenatally detected mild dilatation and to document the natural history of this ultrasound finding in postnatal life, we formally evaluated the outcome of 29 children (39 dilated kidneys) at a mean period of follow up of 4.2 years [30]. During this cumulative total of 122 child years of follow up, we documented only two episodes of urological morbidity, i.e. one symptomatic UTI in a girl who had previously undergone a negative voiding cystogram and an unexplained episode of hematuria in a second child. When the 39 mildly dilated kidneys were re-evaluated with ultrasound at a mean of 4.2 years, 27 (69%) were entirely normal and no longer dilated. Twelve kidneys (31%) had persisting dilatation but this was either unchanged or improved. We did not encounter a single case of increasing dilatation.

Despite hopes to the contrary there is little reason to believe that mild dilatation would serve as a reliable ultrasound marker with which to screen for vesicoureteric reflux. Attempts to screen for VUR with ultrasound in postnatal life have been plagued by false positive and false negative findings. If anything, prenatal ultrasound is likely to prove even less reliable.

Vesicoureteric reflux

Grades of reflux which are associated with detectable dilatation can sometimes be picked up on prenatal ultrasound. A postnatal cystogram is of course required to confirm the diagnosis and to distinguish between reflux and obstruction. In contrast to the published experience of clinically presenting reflux in which females predominate, infants whose VUR has been detected prenatally are mainly males. In 6 [1,4,13,25,26,28] published series totalling 141 prenatally detected cases, 118(84%) were males. Although high grade primary VUR in male infants is generally regarded as a primarily anatomical phenomenon (related to an embryological abnormality of the ureterovesical junction) some intriguing work by Hjälmås and his colleagues [27] has challenged this view. Urodynamics on 6 male infants between 3 weeks and 9 months of age revealed unexpectedly high intravesical pressures, i.e. 100 cm to 234 cm during voiding. It is possible that even in the absence of urethral obstruction, abnormal voiding dynamics in utero may play a role in the aetiology of

VUR in males. Functional imaging with 99mTc DMSA offers an opportunity to study renal function and morphology in refluxing units which have never been exposed to infection. The evidence of early DMSA studies is somewhat conflicting but tends to confirm the view that whilst renal damage seen in children presenting with urinary infection often includes a congenital component, acquired infective scarring plays a more important role [6,26]. A higher rate of spontaneous resolution of VUR has been reported[1,4,13,28] in prenatally detected cases than would be expected for comparable rates of VUR presenting clinically. This observation combined with the technical problems of re-implanting wide ureters into an infant bladder, represents a powerful argument for conservative management in the first instance. Anecdotal evidence is accumulating, however, to point to a possible benefit from circumcision in boys with prenatally detected VUR -but this has yet to be substantiated by a formal trial.

Pelvi-ureteric junction obstruction

Numerically PUJ obstruction represents the most important uropathy detected by prenatal ultrasound, accounting for 30-50% of all significant prenatally detected uropathies. The management of prenatally detected PUJ obstruction has become the most contentious issue in pediatric urology. Whilst some massive hydronephroses are associated with a visible or palpable abdominal mass, the overwhelming majority of hydronephroses are now being detected in asymptomatic outwardly normal infants. Ransley [22], Koff [17] and others have demonstrated that in some situations isotopically confirmed obstruction has the capacity to resolve spontaneously in postnatal life. For these reasons a more selective approach to early pyeloplasty has evolved in recent years. In most major centres the indications for early pyeloplasty are based on the following:

1. Ultrasound appearances. A loose correlation exists between severity of hydronephrosis and functional impairment.
2. Isotope renography. Although drainage curve data are widely used in the diagnosis of obstruction, Ransley and Manzoni [23], highlighting the technical difficulties in interpreting drainage curves in infancy, have suggested an alternative policy based on differential renal function. According to Ransley and Manzoni, hydronephrotic kidneys with well-preserved function, i.e. differential function >40% can be managed conservatively despite the presence of proven obstruction. In the presence of functional impairment (approximately one third of prenatally detected PUJ obstructions) early pyeloplasty is indicated.
3. Intravenous urography. Many surgeons still insist on seeing an IVU before proceeding to pyeloplasty.

A selective approach based on a combination of diagnostic modalities is likely to result in an early pyeloplasty rate of 30-40% rising to 50-60% when cases coming to pyeloplasty in later childhood are included in the calculations. Although appropriate conservative management is associated with a small risk of loss of function during the period of observation this is probably an acceptable alternative to unnecessary pyeloplasty in large numbers of children in whom the condition would otherwise have resolved spontaneously. Many issues surrounding prenatally detected PUJ obstruction remain unresolved and careful longterm studies are required to shed further light on the natural history of this condition.

Multicystic dysplastic kidney

The routine use of ultrasound in pregnancy has demonstrated that this is a far more common anomaly than was previously suspected. In the past a multicystic kidney generally presented as an abdominal mass in the neonatal period. More than 80% of the lesions being identified on prenatal ultrasound are clinically undetectable at birth [12]. In an analysis of 43,230 pregnancies in our institution we derived an incidence of 1:4 300 for liveborn infants. Diagnostic difficulties can arise in distinguishing multicystic dysplasia from gross hydronephrosis but the total absence of function on DMSA scan usually confirms the diagnosis of multicystic dysplasia. The case for a routine voiding cystogram is supported by the findings of Flak et al [11] who documented a 28% incidence of contralateral VUR into the solitary functioning kidney. Sixty five of the 441 children with multicystic kidney reported to the Multicystic Dysplastic Kidney Registry [31] underwent voiding cystography and VUR was identified in 43%.

The arguments for the prophylactic removal of asymptomatic multicystic dysplastic kidneys central on the perceived risks of hypertension and malignancy. (These issues are considered in more depth in the article on Multicystic Dysplastic Kidneys by SJ Cohen.) The spontaneous involution of multicystic dysplastic kidneys, both in pre and postnatal life is well documented [21] and it seems probable that this process accounts for a substantial proportion of apparent instances of unilateral renal agenesis discovered in adult life.

Posterior urethral valves

Prenatal ultrasound is revealing the "hidden mortality" at the severe end of the pathological spectrum of this condition with the consequence that pediatric urologists are now becoming involved in management decisions on severely affected newborns with renal dysplasia and pulmonary hypoplasia. In our experience [16] the early appearance of dilatation is a significant predictor of poor functional outcome. Of 31 cases of prenatally detected posterior urethral valves dilatation was evident at or before 24 weeks in 17, of whom 4 died in the neonatal period and 5 are currently in chronic renal failure. Fewer than half the boys in this group are alive with a normal plasma creatinine. In contrast, in the group of 14 cases of prenatally detected posterior urethral valves with normal ultrasound appearances during the second trimester, there were no neonatal deaths and only 1 boy has evidence of impaired renal function, whilst the remaining 13 boys in this group (93%) are alive with normal plasma creatinine values on follow up.

Prenatal detection facilitates prompt treatment in postnatal life and avoids the overwhelming sepsis, acidosis and acute renal failure in infancy with which the condition commonly presented in the past. Whether prompt treatment and the prevention of pyelonephritis and systemic sepsis in infancy will be reflected in an improved longterm prognosis for renal function is unclear.

Conclusion - lessons learned

1. A substantial proportion of non lethal fetal uropathies are undetectable on second trimester ultrasound. Those that are detected tend to represent the severe end of the obstructive spectrum.

2. The theoretical benefits of fetal intervention have not been translated into clinical reality. Fetal intervention should be limited to a handful of specialist centers, the results of complications carefully monitored and honestly reported.

3. Mild dilatation of the renal pelvis is a common ultrasound finding of doubtful clinical significance. Invasive investigation, particularly voiding cystography, is not routinely justified.

4. Investigation and postnatal management of prenatally detected PUJ obstruction remains controversial. The available evidence supports a selective approach to early pyeloplasty based on a combination of ultrasound and isotope findings.

5. Asymptomatic prenatally detected multicystic dysplastic kidneys can be safely left in situ.

6. The long term benefits, if any, of prenatal detection of posterior urethral valves remain unproven but prenatal detection has contributed to the substantial reduction in sepsis-related morbidity and mortality in recent years.

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