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Review article

Fetal bladder outlet obstruction: Embryopathology, *in utero* intervention and outcome

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Summary
Fetal bladder outlet obstruction (BOO), most commonly caused by posterior urethral valves (PUV), remains a challenging and multi-faceted condition. Evolving techniques, and refinement in ultrasound, optics and instrumentation, have increased our rate of prenatal diagnosis, and enabled valve ablation not only in smaller newborns, but also in fetuses. Long-term outcome studies have raised our awareness of the silent damage caused by bladder dysfunction and polyuria and encouraged their proactive management. In spite of our best efforts, the proportion of boys with PUV who progress to chronic and end-stage renal disease (ESRD) has not changed in the last 25 years. Evidence suggests a reduction in perinatal mortality following prenatal intervention, probably resulting from amelioration of oligohydramnios at the crucial time of lung development between 16 and 28 weeks' gestation, but no improvement in postnatal renal outcome. There are no bladder functional outcome studies in patients who have undergone prenatal intervention and hence the long-term effect of *in utero* defunctionalisation of the bladder is not known. This aim of this review is to revisit the embryopathology of fetal BOO, in particular the renal and bladder structural and functional changes that occur with *in utero* obstruction. The effect of earlier prenatal diagnosis, and therapy, on postnatal outcome is also explored and compared with outcomes published for traditional postnatal treatment.

Introduction

The incidence of congenital lower urinary tract obstruction is estimated to be 2.2 in 10,000 births, with up to 62% being diagnosed prenatally. About 20% of cases are associated with other structural or chromosomal anomalies [1]. The most common underlying diagnoses are posterior urethral valves (PUV), urethral atresia or the Prune Belly Syndrome (PBS) [2]. The incidence of PUV appears to be stable with a total prevalence of 3.34 (2.95–3.72) per 10,000 births. Less common causes of congenital BOO include anterior urethral valves/anterior urethral diverticulum; prolapsed ureterocoele; syringocoele; megalourethra; megacytis-microcolon-hypoperistalsis syndrome; obstruction by a hydrocolpos in females with cloacal anomalies; or rarely obstruction by a tumour such as a sacro-coccygeal teratoma. The 17th Report of the UK Renal Registry published in 2014 confirmed obstructive uropathy as the second commonest cause (18%) of paediatric end-stage renal disease (ESRD) after renal dysplasia ± reflux (34%). The percentage of children with obstructive nephropathy was 18.0% between 2009 and 2013 [3].

Embryopathology

The earliest descriptions of PUV are credited to Morgagni (1717) and Langenbeck (1802), who commented on valve-like folds in autopsy specimens. Tolmatschew described the valves as "overgrowths of the normally present folds and ridges in the urethra", disputed by Bazy, who suggested that the valves were a persistence of the urogenital membrane that separated the anterior and posterior urethra prior to the process of canalisation [4]. Lowsley noted that the PUV originated from the same connective tissue that encased the ejaculatory ducts as they coursed through the prostate, and went on to attach to the entire circumference of the urethra. The fibres were stratified, rather than transitional, epithelium, suggesting an origin from the mesonephric ducts. Thus the putative origin of PUV as an anomaly of the insertion of the mesonephric ducts into the prostatic urethra [4]. In 1919, Young et al. attempted to unify these theories by offering a classification of PUV: type 1 valves, the most common, were composed of a ridge coursing anterior from the distal verumontanum, dividing into two leaflets and attaching to the anterior urethra; type 2

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valves, the most rare, extended from the proximal verumontanum toward the internal sphincter and bladder neck; type 3 valves attached to the entire circumference of the urethra with a central opening. This anatomical distinction was challenged by Dewan et al. in the early 1990s, who argued that the obstruction was caused by a membrane rather than valves, hence the term "congenital obstructive urethral membrane" (COPUM). Dewan et al. proposed two distinct causes of posterior urethral obstruction: COPUM and Cobb's collar, based on their relationship to the verumontanum. COPUM was thought to be an oblique membrane intimately associated with the distal verumontanum, and Cobb's collar (or congenital urethral stricture) a transverse membrane located distal to the external urethral sphincter.

The Prune Belly Syndrome (PBS) or Triad Syndrome, as described by Eagle and Barrett [5], is thought to be caused by an "abnormal angulation" of the urethra in a region where the prostate has incompletely developed, and this may in itself impair urine flow [6,7], rather than complete mechanical obstruction. However, a PBS phenotype may be seen in cases with urethral atresia, which may support the hypothesis that early BOO with massive bladder distension or ascites can result in atrophy of the abdominal wall musculature, induce renal dysplasia and impair testicular descent. The appearance of urethral atresia has been described as a completely obstructed membrane below the verumontanum with a hypoplastic distal urethra.

Distal urethral obstruction is less common and may be caused by "anterior urethral valves" (AUV), which are thought to be the edges of a ruptured syringocele (cystic dilatation of Cowper's Gland, which may also be a cause of BOO). The megacystis-microcolon syndrome (MMS), a generalised disorder of peristalsis with absent ganglion cells in the bladder wall, can also manifest as congenital BOO [8,9].

The effect of congenital BOO on the rest of the urinary tract is less well understood and has led to the development of a number of animal models [10]. Obstructive nephropathy is typically characterised by small cortical cysts, fewer layers of glomeruli than normal (renal hypoplasia) and a disorganised medulla (renal dysplasia). It is debated whether the kidney malformations are secondary to impairment of fetal urine flow or are manifestations of a primary defect which affects the development of the entire urinary tract, from the kidney to the urethra [11] — the likelihood is a combination of both. Evidence from the fetal lamb model suggests that damage caused by urethral and urachal occlusion is greater the earlier in gestation obstruction is initiated and the longer it is maintained [12,13]. Early on in the obstructive process, bladder detrusor muscle architecture and function is maintained, but the effect on the obstructed kidneys is more acute, with evidence of hydronephrosis, cortical cysts with glomerular tufts and dilated medullary ducts (Fig. 1). On prolonged obstruction, the bladder wall becomes "thinned"

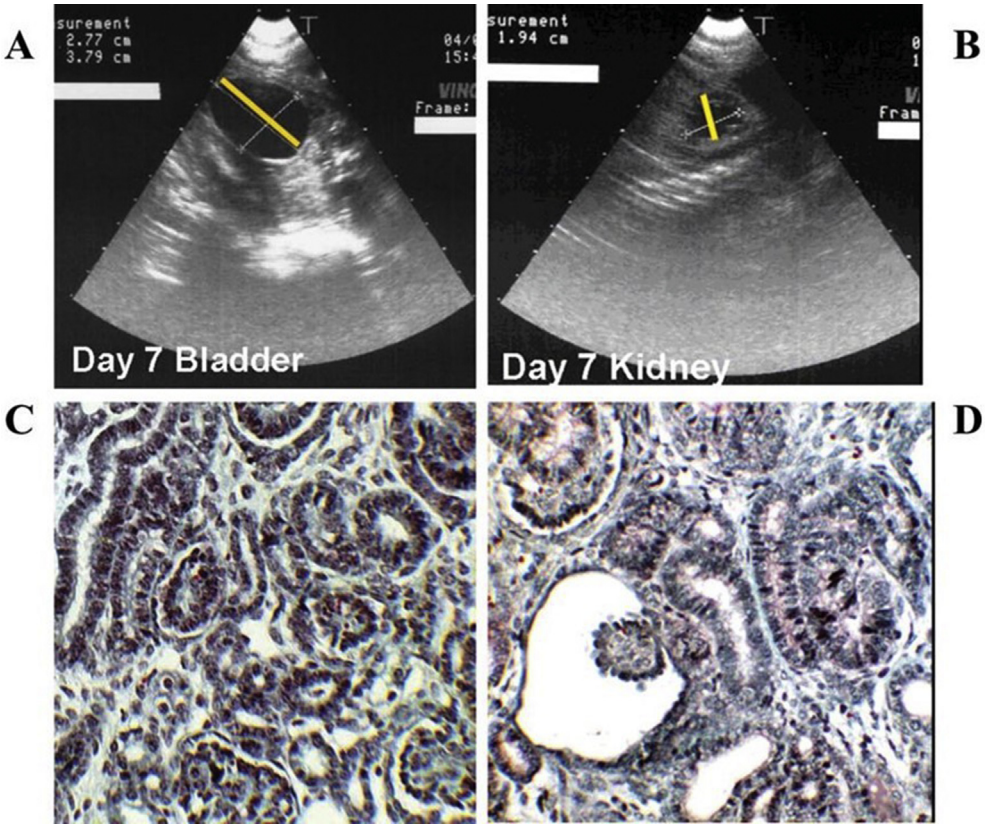

Figure 1 Appearance of the fetal urinary tract following 1 week urachal and urethral obstruction in the fetal lamb at mid-gestation. (A) dilated fetal bladder with (B) hydronephrosis. Histology of a sham kidney (C) with an intact cortex and non-dilated nephrons in contrast to an obstructed kidney (D) exhibiting cortical cysts, glomerular tufts and dilated tubules. Data adapted from Farrugia MK, MD Thesis (University of London, 2008).