Fetal urine biochemistry in the assessment of obstructive uropathy

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In 60 fetuses with obstructive uropathy, sodium, total calcium, urea, and creatinine were measured in samples obtained by "urodochocentesis" or pyelocentesis at 16 to 36 weeks' gestation. The patients were retrospectively assigned into two groups on the basis of outcome. Group 1 (n = 20) included infants who either had normal postnatal renal function or absence of prenatal renal dysplasia. Group 2 included infants who either had histologic evidence of renal dysplasia or subsequently developed renal failure. In group 1 the urinary sodium decreased and creatinine increased with gestation, demonstrating maturation in fetal renal function. In group 2 the urinary sodium and calcium were higher and the urinary urea and creatinine were lower than in group 1. The best predictor of outcome was the combination of either high calcium or high sodium with a positive predictive value of 91.3% and negative predictive value of 77.7%. In the antenatal evaluation of obstructive uropathy, fetal urinary biochemistry provides useful information for more accurate counseling of the parents and a rational basis for selecting patients who may benefit from intrauterine therapeutic interventions. (Am J Obstet Gynecol 1992;166:932-7.)

Key words: Fetal urine, fetal obstructive uropathy, urodochocentesis, pyelocentesis, ultrasonographic diagnosis

Prenatally, several parameters have been used in the evaluation of renal function in fetuses with obstructive uropathy, including amniotic fluid volume, ultrasonographic appearance of kidneys, and biochemical composition of fetal urine. The latter provides the most accurate information, and poor renal function is inferred from the findings of a high urinary sodium level (>100 mmol/L) and low urinary urea (<6 mmol/L) and creatinine (>150 μmol/L) levels.[1, 2]

In a retrospective study of 40 fetuses with obstructive uropathy Crombleholme et al.[1] reported that a urine sodium level of >100 mmol/L was predictive of poor prognosis, whereas a sodium level of <100 mmol/L was associated with good renal function. Similarly, Grannum et al.[3] measured urinary sodium in 12 fetuses with obstructive uropathy and demonstrated that the four fetuses with levels <100 mmol/L had either normal neonatal renal function or no evidence of renal dysplasia, whereas the eight fetuses with levels >100 mmol/L had renal dysplasia.

In contrast, Wilkins et al.[4] and Elder et al.[5] reported that fetal urine electrolytes are not accurate predictors of outcome. Thus in their combined series of 13 fetuses with obstructive uropathy only four of the seven with urinary sodium levels >100 mmol/L had poor outcome or histologic evidence of renal dysplasia, and only one of the six fetuses with levels <100 mmol/L had good renal function after birth.

One possible explanation for the apparent discrepancy in results is that in these studies no consideration was given for the gestation at which their fetuses were sampled; animal studies have demonstrated that the composition of fetal urine changes with gestation.[6, 7]

The aim of this study was to establish reference ranges with gestation for fetal urine sodium, calcium, urea, and creatinine and to examine the value of these substances in predicting the outcome of 60 fetuses with obstructive uropathy.

Patients and methods

In 60 fetuses with obstructive uropathy, urine samples were obtained by "urodochocentesis" (n = 52) or pyelocentesis (n = 8) at 16 to 36 weeks' gestation and sodium, total calcium, urea, and creatinine levels were measured on a multichannel, continuous-flow analyzer (SMAC II, Technicon, Basingstoke, United Kingdom). Urodochocentesis and pyelocentesis involve the ultrasonographically guided transabdominal insertion of a 20-gauge needle into the fetal bladder or renal pelvis, respectively, and the aspiration of urine. Urodochocentesis was performed when the fetal bladder was dilated and the ultrasonographic appearance of the two kidneys was similar. Pyelocentesis was performed when there was unilateral pelvicaliceal dilatation. In all cases fetal blood sampling and cytogenetic analysis demon-

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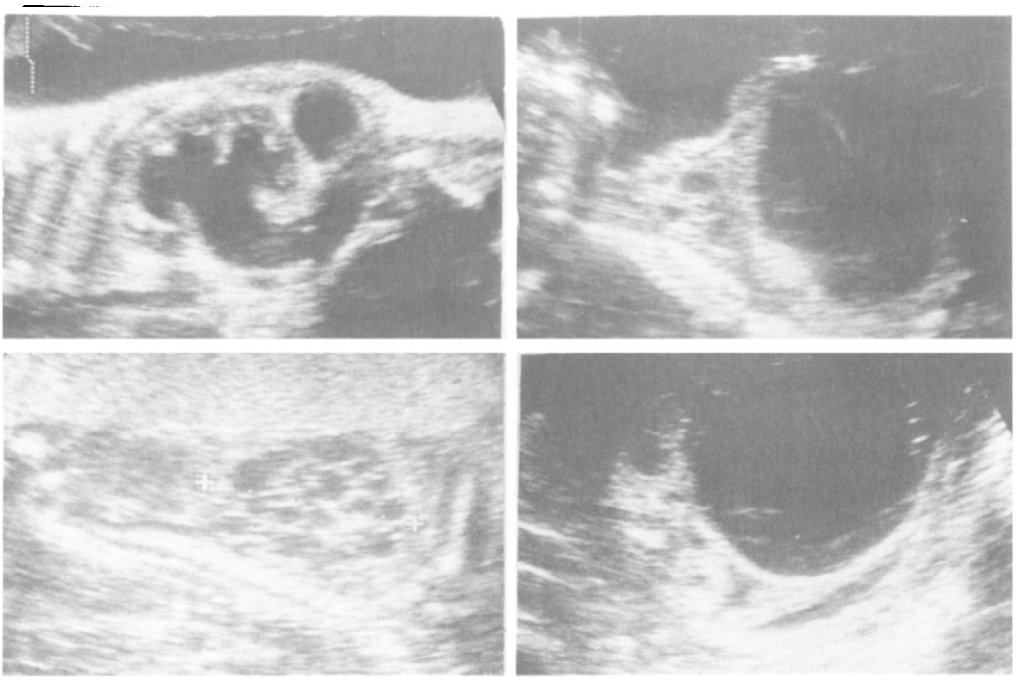

Fig. 1. Ultrasonographic appearance of fetal hydronephrosis with moderate-to-severe pelvicaliceal dilatation *(top left)*, multicystic dysplasia *(bottom left)*, and mild hydronephrosis with hyperechogenic cortex; longitudinal section shows dilated bladder *(top right)* and transverse section shows dilated bladder and echogenic kidneys *(bottom right)*.

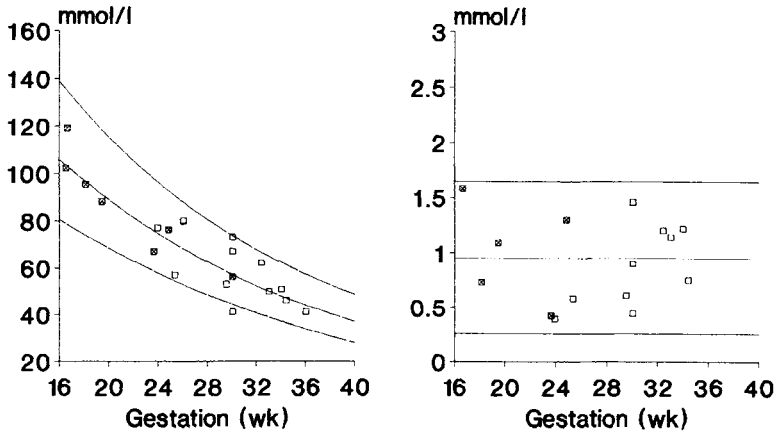

Fig. 2. Reference ranges (mean, 95th and 5th percentiles) with gestation for urinary sodium *(left)* and calcium *(right)* concentrations, calculated from study of fetuses with obstructive uropathy who either survived with normal postnatal renal function (□) or died but had no histologic evidence of renal dysplasia (⊠).

strated a normal karyotype. The current study does not include data from fetuses who underwent vesicoamniotic shunting because this may have influenced the natural history of the disease. Similarly, the data from chromosomally abnormal fetuses that were sampled during the same period (1984 through 1990) are excluded.

Ultrasonographically the fetal kidneys were subdivided into three groups: (1) hydronephrotic with moderate-to-severe pelvicaliceal dilatation, $n = 40$; (2) multicystic dysplastic with multiple noncommunicating cysts of variable size and irregular, hyperechogenic stroma, $n = 9$; (3) mildly hydronephrotic with hyperechogenic cortex, $n = 11$ (Fig. 1). The latter type is commonly found in the presence of a grossly dilated bladder, usually before 20 weeks; in those cases where vesicoamniotic shunting is performed, after 4 to 8 weeks these kidneys usually develop the typical irreg-

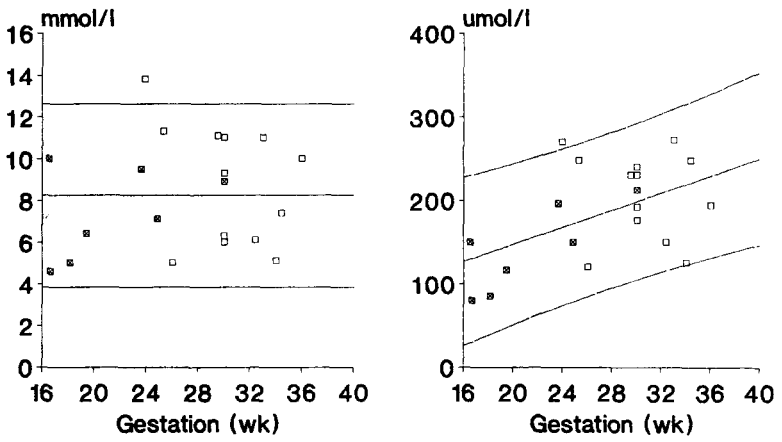

Fig. 3. Reference ranges (mean, 95th and 5th percentiles) with gestation for urinary urea *(left)* and creatinine *(right)* concentrations, calculated from study of fetuses with obstructive uropathy who either survived with normal postnatal renal function (□) or died but had no histologic evidence of renal dysplasia (☒).

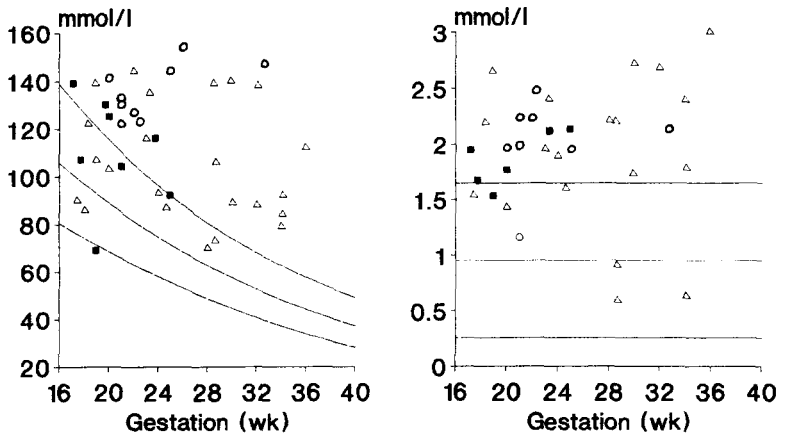

Fig. 4. Urinary sodium *(left)* and calcium *(right)* concentrations in fetuses with obstructive uropathy who either had histologic evidence of renal dysplasia or subsequently showed renal failure plotted on the appropriate reference range (mean, 95th and 5th percentiles) with gestation. Ultrasonographically, fetal kidneys were classified as hydronephrotic with moderate-to-severe pelvicaliceal dilatation (△), multicystic dysplastic (○), or mildly hydronephrotic with hyperechogenic cortex (●).

ular, shrunken, cystic, hyperechogenic appearances found in Potter stage IIb renal dysplasia (unpublished observations).

The 60 patients were retrospectively assigned into two groups on the basis of outcome. In group 1 (n = 20) 13 infants are alive with normal renal function (plasma creatinine concentration <70 μmol/L) at 1 to 6 (mean 2.1) years of age and seven fetuses were electively aborted (n = 6) or died in utero (n = 1) but had no histologic evidence of renal dysplasia. Group 2 (n = 40) includes (1) cases with histologic evidence of renal dysplasia (fetuses that were electively aborted, n = 22; fetuses that died in utero, n = 2; infants who died, n = 7; infants who are alive but required nephrectomy of the kidney sampled in utero, n = 4) and (2) infants who are in chronic renal failure at the age of 1 to 5 (mean 2.6) years (n = 5).

All patients were referred to our unit for diagnosis and further assessment. Subsequent management of the pregnancies was undertaken in the referring hospitals that provided the data on postmortem findings or follow-up of surviving infants.

Results

In group 1 there were significant associations between gestational age and fetal urinary sodium ($\log^{10}$ sodium concentration in millimoles per liter = 2.328 − 0.019 × gestational weeks, residual SD 0.062, r = 0.89, n = 20, $p < 0.0001$) and creatinine (creatinine concentration in micromoles per liter = 45.058 +

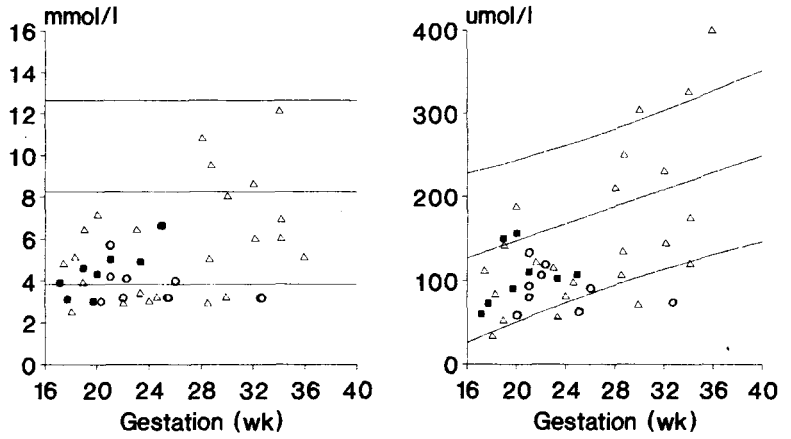

Fig. 5. Urinary urea *(left)* and creatinine *(right)* concentrations in fetuses with obstructive uropathy and either histologic evidence of renal dysplasia or subsequent development of renal failure plotted on appropriate reference ranges (mean, 95th and 5th percentiles) with gestation. Ultrasonographically, fetal kidneys were classified as hydronephrotic with moderate-to-severe pelvicaliceal dilatation (▲), multicystic dysplastic (○), or hydronephrotic with hyperechogenic cortex (●).

Table I. Incidence of oligohydramnios, high (>95th percentile) sodium or calcium levels, and low (<5th percentile) urea or creatinine levels in 60 cases of fetal obstructive uropathy grouped according to good or poor prognosis and subgrouped according to ultrasonographic appearances of fetal kidneys

	Group 1: Good prognosis			*Group 2: Poor prognosis*					
	Total	*Moderate-to-severe hydronephrosis*	*Mild hydronephrosis with hyperechogenic cortex*	*Total*	*Moderate-to-severe hydronephrosis*	*Mild hydronephrosis with hyperechogenic cortex*	*Multicystic dysplasia*	*Positive predictive value*	*Negative predictive value*
Oligohydramnios	5/20	4/17	1/3	25/40	13/23	6/8	8/9	77.8	52.2
Sodium >95th percentile	1/20	1/17	0/3	29/40	15/23	5/8	9/9	94.4	65.2
Calcium >95th percentile	0/17	0/15	0/2	25/33	13/19	5/6	7/8	95.0	71.4
Sodium/calcium >95th percentile	0/20	0/17	0/3	13/40	7/23	2/8	4/9	91.3	77.7
Urea <5th percentile	1/20	1/17	0/3	10/40	6/23	0/8	4/9	83.3	42.8
Creatinine <5th percentile	1/17	1/15	0/2	28/34	15/19	5/7	8/8	100.0	44.4

Positive and negative predictive values were calculated from the 41 cases in which the kidneys showed moderate-to-severe hydronephrosis or mild hydronephrosis with hyperechogenic cortex and all urinary substances were measured; cases of multicystic dysplasia were excluded because ultrasonographic appearances alone were always predictive of poor prognosis.

5.119 × gestational weeks, residual SD 52.463, $r = 0.52$, $n = 20$, $p < 0.05$) but not calcium (mean 0.935 mmol/L, residual SD 0.422) or urea (mean 8.245 mmol/L, residual SD 2.674). Reference ranges for these substances with gestation were established by regression analysis after it was ensured that the data were normally distributed (Figs. 2 and 3).

In group 2 the mean urinary sodium and calcium values were significantly higher ($t = 5.74$, $p < 0.0001$ and $t = 3.4$, $p < 0.01$, respectively) and the mean urinary urea and creatinine values ($t = 4.84$, $p < 0.0001$ and $t = -2.08$, $p < 0.05$, respectively) were significantly lower than in group 1 fetuses (Figs. 4 and 5).

The predictive value of the ultrasonographic appearance of the kidneys, oligohydramnios (no vertical pool of amniotic fluid ≥1 cm), and high (>95th percentile) sodium or calcium levels and low (<5th percentile) urea or creatinine levels are shown in Table I. All cases with multicystic kidneys had a bad outcome (renal dysplasia). However, 3 of the 9 (33%) fetuses with mildly hydronephrotic, hyperechogenic kidneys

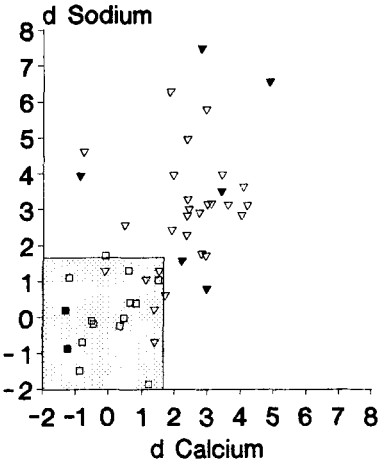

Fig. 6. Urinary sodium and calcium concentrations (expressed as numbers of standard deviations from appropriate normal mean for gestation) in fetuses with obstructive uropathy and either good (□) or poor (◇) prognosis. In 35 of 40 cases from poor prognosis group either sodium or calcium concentration was >95th percentile of reference ranges *(shaded areas)*. Biochemical findings of samples obtained from renal pelvis *(filled symbols)* are similar to those of samples from bladder.

and 17 of the 40 (43%) with moderate-to-severe hydronephrosis had a good outcome (no renal dysplasia or good renal function). In the latter two groups the best predictor (positive and negative predictive value) of outcome was the combination with either high calcium or high sodium (Fig. 6). There was no obvious difference in biochemical results of samples obtained by pyelocentesis and urodochocentesis.

Comment

This study establishes that in fetuses with obstructive uropathy and either normal postnatal renal function or absence of prenatal renal dysplasia the urinary sodium level decreases and the creatinine level increases with gestation, whereas values of calcium and urea do not change. In fetuses with obstructive uropathy and either histologic evidence of renal dysplasia or subsequent development of renal failure the urinary sodium and calcium levels are higher and the urinary urea and creatinine levels are lower than in the good prognosis group.

The concentration of urinary electrolytes and solutes in the good prognosis group, from which the reference ranges were established, is not necessarily representative of urinary biochemical findings in normal fetuses. However, establishment of normal ranges would be impossible. Furthermore, in the prenatal assessment of a fetus with obstructive uropathy it may be preferable to evaluate urinary biochemical levels in relation to reference ranges from fetuses with obstructive uropathy and good outcome rather than from normal fetuses.

Nevertheless, the number of cases used for construction of the reference ranges is small and the end points for inclusion are heterogeneous; lack of histologic evidence for intrauterine renal dysplasia in 7 of the 20 cases does not necessarily imply normal postnatal renal function. Furthermore, plasma creatinine levels of <70 μmol/L at 1 to 6 years does not guarantee that good renal function will persist. Indeed, in children with obstructive uropathy good renal function in the first few years of life is not necessarily predictive of good long-term outcome.[8] Therefore to establish more reliable reference ranges it will be necessary to undertake a multicenter study involving large numbers of fetuses with obstructive uropathy undergoing urodochocentesis, but not vesicoamniotic shunting, and surviving with normal renal function after long-term follow-up.

The urinary biochemical findings in the good prognosis group demonstrate a gestation-related maturation in fetal renal function. In normal urine production there is tubular reabsorption of sodium from an ultrafiltrate of serum. The fetal plasma sodium level is the same as that of the mother and does not change with gestation; therefore the observed decrease in urinary sodium concentration with gestation presumably reflects maturation in tubular reabsorption. Lind et al.[9] obtained fetal urine samples at hysterotomy for elective abortion at 12 to 22 weeks' gestation and demonstrated that as early as 12 weeks the kidney has considerable ability to resorb sodium. The high urinary sodium levels in fetuses with renal dysplasia are indicative of either tubular damage, presumably caused by the obstruction or primary maldevelopment of the kidneys, which is the most likely explanation for multicystic dysplasia.

Although calcium is also resorbed in the tubules, the fetal urinary concentration does not normally decrease with gestation. The most likely explanation for this finding is that increased tubular resorption with gestation is counterbalanced by the rising concentration of ionized calcium in fetal plasma and therefore in glomerular ultrafiltrate.[10, 11] Alternatively, the maximum resorptive capacity for calcium is fully established by 16 weeks' gestation because calcium is essential for fetal growth and development. The fetal hormone responsible for the strong conservation of calcium is probably parathyroid-related peptide, which is expressed in the fetal kidney as early as 12 weeks.[12] The high urinary calcium concentration in fetuses with renal dysplasia is likely a consequence of both impaired tubular resorption and proteinuria with loss of ionized and protein-bound fractions, respectively.

There is no significant renal resorption or secretion of creatinine, and the urinary concentration of this solute is merely a reflection of tubular resorption of water. The gestation-related increase in urinary creatinine concentration is likely a consequence of maturation of renal tubular function. In fetuses with renal dysplasia the urinary creatinine concentration is lower because

tubular resorption of water is impaired. However, a low creatinine level is not as sensitive a predictor of renal dysplasia as increased sodium or calcium levels. A possible explanation for this is that urinary creatinine concentration reflects not only tubular function but also the gestation-related increasing fetal plasma concentration.[13] This is dependent on muscle mass, which is unlikely to be affected by the degree of renal damage.

The urinary urea concentration does not change with gestation and is approximately three times higher than in fetal plasma.[9] This is unlike urinary sodium, which decreases because of active tubular resorption, or urinary creatinine, which increases because of active water resorption. In renal dysplasia electrolyte and water resorption are impaired, resulting in urinary urea concentrations that approach plasma levels.

In the antenatal evaluation of obstructive uropathy,the ultrasonographic finding of multicystic kidneys is associated with renal dysplasia; abnormal urinary biochemical findings merely confirm poor renal function. In contrast, in hydronephrosis both the degree of pelvicaliceal dilatation and the amniotic fluid volume are poor predictors of outcome; urodochocentesis or pyelocentesis with measurement of sodium, calcium, urea, and creatinine provides useful information for more accurate counseling of the parents. Furthermore, fetal urinary biochemical findings provide a rational basis for selecting patients who may benefit from vesicoamniotic shunting or other intrauterine urinary diversion procedures and allows evaluation of the possible effectiveness of such therapeutic interventions.

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