Fetal Urine Cystatin C as a Predictor of Postnatal Renal Function in Bilateral Uropathies

To the Editor:
Fetal obstructive uropathies are among the most frequent anomalies diagnosed by prenatal ultrasound. Prenatal management of obstructive uropathies depends on the evaluation of renal function. Although the prognosis is good in unilateral cases, bilateral uropathies are associated with a wide spectrum of outcomes ranging from perinatal death from pulmonary hypoplasia and terminal renal failure to survival with normal renal function. In the mildest cases and in the most severe forms of fetal uropathy, sonography alone is a good predictor of outcome, and invasive approaches based on fetal blood or fetal urine biochemistry are therefore unnecessary. In contrast, in bilateral uropathies with normal amniotic fluid volume or moderate oligohydramnios and without major structural anomaly of the renal parenchyma, neonatal survival is expected, but postnatal morbidity is difficult to predict by sonography alone (1–3).

In the fetus, serum creatinine cannot be used as a marker of glomerular filtration rate (GFR) because it crosses the placenta and is cleared by the mother (4). Fetal serum β₂-microglobulin has been evaluated in a few cases, but more experience is necessary (5–7). Fetal urinalysis is probably the most accurate approach to quantitative evaluation of renal function. This is because during fetal life, the mother supplies the fetus through the placenta with balanced nutrients, and fetal homeostasis is ensured without the intervention of the fetal kidneys. Therefore, the composition of fetal urine depends only on fetal renal function and reflects renal potential. Although sodium is the most widely used fetal urinary marker, we have shown previously that other compounds (chloride, calcium, phosphorus, β₂-microglobulin, and proteins) are also of interest (1, 8). Of these, fetal urine sodium and β₂-microglobulin, which correlate the best with postnatal renal outcome, reflect tubular damage rather than glomerular filtration. Recently, serum cystatin C has been proposed as a marker of GFR in children and adults (9–14). Cystatin C, with a molecular mass of 13.3 kDa, does not cross the placenta, is filtered by the glomerulus and reabsorbed and metabolized by the tubule, and is therefore absent from urine. The aim of this study was to evaluate the potential value of fetal urine cystatin C in predicting postnatal serum creatinine at 1 year in children with a prenatal diagnosis of bilateral obstructive uropathy.

Cystatin C was retrospectively assayed in 71 aliquots of frozen fetal urine samples. These aliquots had not been frozen and thawed previously. In all cases, the fetus was affected by bilateral obstructive uropathy without any other associated malformation. The postnatal outcome was known in all cases. Patients were retrospectively divided into three groups based on the degree of defined renal function: group 1, severe renal failure, leading to death (19 cases: 17 terminations of pregnancy with marked oligohydramnios with hyperechogenic parenchyma, and 2 neonatal deaths from acute pulmonary hypoplasia and renal failure; renal dysplasia confirmed postmortem in all 19 cases); group 2, moderate renal failure, serum creatinine (Jaffe method) at 1 year >50 μmol/L (19 cases); and group 3, normal renal function, serum creatinine at 1 year <50 μmol/L (33 cases). In all cases, detailed sonography specifying the level of obstruction, amniotic fluid volume, and renal parenchymal structure was performed. Fetal urine cystatin C was measured by particle-enhanced immunonephelometry (BNA; Dade-Behring, Marburg, Germany) (13). Fetuses with bilateral obstructive uropathy but with normal serum creatinine at 1 year can be considered as normal. Therefore, in this group we analyzed the relation of cystatin C to gestational age. No change was observed between 23 and 37 weeks of amenorrhea.

Cystatin C was significantly higher (P <0.001) in the group with severe renal failure (median ± SE, 4.1 ± 0.76 mg/L; range, 0.45–13.1 mg/L) than in the two other groups, and differences between group 2 (median ± SE, 0.47 ± 0.27 mg/L; range 0.05–4.75 mg/L) and group 3 (median ± SE, 0.05 ± 0.05 mg/L; range 0.05–1.09 mg/L) were also statistically significant (P = 0.0006; Fig. 1). The best sensitivity (84%) and specificity (84%) in predicting severe renal failure (group 1 vs groups 2 + 3) were obtained using a cutoff at 1 mg/L. With the same cutoff, the sensitivity of cystatin C in distinguishing group 2 from group 3 was 37% with a specificity of 97%. There was a significant correlation between fetal urinary cystatin C and postnatal serum creatinine at 1 year (Spearman correlation coefficient ρ = 0.66; P <0.0001).

When a cutoff at 5 mg/L was used, the sensitivity of β₂-microglobulin in predicting severe renal failure was 100% with a specificity of 82%. With the same cutoff, the sensitivity of β₂-microglobulin in distinguishing group 2 from group 3 was 50% with a specificity of 94%. The correlation between fetal urinary β₂-microglobulin and postnatal serum creatinine at 1 year was the same as for cystatin C (Spearman correlation coefficient ρ = 0.70; P <0.0001).

When a cutoff at 75 mmol/L was used, the sensitivity of sodium in predicting severe renal failure was 100% with a specificity of 98%. With the same cutoff, the sensitivity of sodium in distinguishing group 2 from group 3 was 5% with a specificity of 100%. The correlation between fetal sodium and postnatal se-
urinary sodium, distinguishing group 2 from group 3. 21% and a specificity of 97% in distinguishing both abnormal amniotic fluid volume and abnormal parenchymal (19 cases); group 2, infants with postnatal serum creatinine >50 µmol/L (19 cases); group 3, infants with postnatal serum creatinine ≤50 µmol/L (33 cases).

Serum creatinine at 1 year was not significant (Spearman correlation coefficient $\rho = 0.36$).

Prenatal ultrasound signs associating both abnormal amniotic fluid volume and abnormal parenchymal structure had a sensitivity of 98% and a specificity of 92% in distinguishing group 1 but a sensitivity of 21% and a specificity of 97% in distinguishing group 2 from group 3.

In summary, all of the indicators we studied—ultrasound signs, fetal urinary sodium, $\beta_2$-microglobulin, and cystatin C—have the same sensitivity and specificity in distinguishing severe renal failure, confirming that ultrasonography is reliable in defining this poor prognosis. However, for distinguishing postnatal renal failure and good renal function, both ultrasound signs and fetal urinary sodium are inefficient, whereas $\beta_2$-microglobulin and cystatin C are equally valuable and are both correlated with postnatal serum creatinine at 1 year. Cystatin C has the advantage over $\beta_2$-microglobulin of not varying with gestational age. As for $\beta_2$-microglobulin, the urinary concentration of cystatin C also increases in uropathies with renal damage, likely as a consequence of the alteration of reabsorption and catabolism by the damaged tubule, thereby demonstrating tubule damage. Although serum cystatin C has recently been shown to be an accurate marker of GFR in adults and infants, fetal urine cystatin C can be considered as a marker of fetal renal tubule damage rather than a marker of GFR.

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References


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Antibody Selection for the Abbott AxSYM Troponin I Assay

To the Editor:

A recent report by Apple et al. (1) presented the performance characteristics of the AxSYM Troponin I (cTnl) assay, which included method comparison data with the Dade-Behring Stratus, Behring Opus, and Beckman Access cTnl assays. In commenting on the absolute differences in measured cTnl between methods...