
Fetal Serum β 2-Microglobulin Before and After Bladder Shunting: A 2-Step Approach to Evaluate Fetuses With Lower Urinary Tract Obstruction

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Purpose: The evaluation of renal function in fetuses with lower urinary tract obstruction by analysis of electrolytes and β 2-microglobulin in fetal urine has limitations. We measured fetal serum β 2-microglobulin before and after bladder shunting to evaluate renal function.

Materials and Methods: A total of 12 fetuses with lower urinary tract obstruction underwent vesicoamniotic shunting. In addition to the standard evaluation of urinary electrolytes and β 2-microglobulin, fetal renal status was assessed by pre-shunt and post-shunt fetal serum β 2-microglobulin.

Results: At 2 to 4 weeks after shunting 2 of the 12 fetuses had persistent oligohydramnios, demonstrated increased values of serum β 2-microglobulin and were confirmed to have renal dysplasia. In the remaining 10 fetuses there was reaccumulation of amniotic fluid for a minimum of 4 weeks after shunting. Serum β 2-microglobulin values increased after shunting in 4 fetuses, all of which developed renal failure, whereas serum β 2-microglobulin did not change or was decreased after shunting in 6, of which 4 had normal renal function at latest followup.

Conclusions: Urinary electrolytes, urinary β 2-microglobulin and pre-shunt serum β 2-microglobulin, whether increased or normal, failed to be predictive of potential response to prenatal intervention. Serial samples of fetal blood may provide distinction between patients who do and do not respond to prenatal treatment of lower urinary tract obstruction.

Key Words: fetus, urinary bladder neck obstruction, prenatal diagnosis, beta 2-microglobulin

The use and effectiveness of surgical intervention for fetal lower urinary tract obstruction remain controversial. Of 169 successful placements of vesicoamniotic shunts reported and reviewed by Coplen the survival rate was 47%, and only 21% of the infants had normal renal function at followup.¹ Holmes et al reported a mortality rate of 43% and concluded that the sequelae of posterior urethral valves might not be preventable.² More recently, a study including 20 fetuses with oligohydramnios, lower urinary tract obstruction and variable prognoses at prenatal evaluation showed that the majority of survivors had acceptable renal and bladder function at long-term followup.³

Evaluation of fetal urinary tract function is considered integral in assessing whether surgical intervention is appropriate.⁴ Various biochemical indices have been used in this process. Increased levels of electrolytes and β 2-microglobulin in the fetal urine are currently the accepted markers of impaired tubular renal absorption, and, hence, renal damage and poor prognosis.^{5,6} However, the correlation between these prenatal indices and postnatal outcome is poor, perhaps due to the inability to reassess renal function after a shunt has been placed. In fact, shunt placement results in continued bladder drainage that prevents further urine sampling for monitoring the evolution of renal function. Another explanation for the poor accuracy of prenatal indi-

ces might be the fact that renal damage is not solely related to urinary tract obstruction, and correction of obstruction fails to stop the progression of damage.

In this study we evaluated the usefulness of serial serum β 2-microglobulin levels to examine if they could provide more accurate assessment of fetal urinary tract status. Serum β 2-microglobulin is an index of glomerular filtration rate. Since it does not cross the placental barrier, increased fetal serum levels indicate glomerular damage.^{7,8} One would expect that relief of obstruction would result in amelioration of renal function. However, this will not be the case if damage has already occurred or if it is unrelated to the obstruction itself.

MATERIALS AND METHODS

A total of 12 fetuses with oligohydramnios and megacystis were referred during the years 1999 to 2006 for diagnostic evaluation at 14 to 30 weeks of gestation. Initial evaluation included detailed ultrasound examination and assessment of urinary electrolytes and β 2-microglobulin. Four fetuses referred before 18 weeks of gestation underwent serial urine sampling. No fetus had other structural abnormalities, but all had mildly hyperechogenic kidneys and bilateral hydronephroses. These findings, together with a bell-shaped bladder and a male phenotype, were consistent with the diagnosis of posterior urethral valves.

After assessment and counseling all women opted for placement of fetal vesicoamniotic shunts. All had been advised that the prognosis was uncertain, and all were aware of the potential risks associated with in utero intervention.

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All fetuses underwent blood sampling immediately before shunting for rapid karyotyping and measurement of serum $\beta 2$ -microglobulin. Intrauterine vesicoamniotic shunting was performed under ultrasound guidance and local anesthesia, using a double pig-tail catheter at a median of 21.5 weeks of gestation (range 18 to 30). Eight women were at 24 weeks of gestation or less at the time of shunting. There were no procedure related complications, and the bladders were decompressed following placement of the shunts in all cases.

The fetuses were reassessed every 2 to 4 weeks until delivery to monitor shunt placement and amniotic fluid volume. To evaluate the effect of shunting on renal function, fetal blood sampling to measure serum $\beta 2$ -microglobulin was performed in the 12 fetuses at 2 to 4 weeks after the bladder diversion.

We analyzed the accuracy of urinary sodium (Na^+) and $\beta 2$ -microglobulin, serum $\beta 2$ -microglobulin (before and after shunting) and amniotic fluid volume after shunting in predicting renal damage at autopsy or postnatally. Published thresholds were used to define abnormal values, including urinary Na^+ greater than 100 mEq/l,⁵ serum $\beta 2$ -microglobulin greater than 4.9 mg/l⁷ and urinary $\beta 2$ -microglobulin greater than 13 mg/l.⁹

RESULTS

Posterior urethral valves were confirmed at autopsy or postnatally in all 12 fetuses/neonates. In 2 cases there was no reaccumulation of amniotic fluid despite successful bladder decompression, and the women opted for termination of pregnancy at 2 and 3 weeks after shunt placement. At autopsy renal dysplasia was confirmed. In the remaining 10 patients amniotic fluid normalized and the shunts were

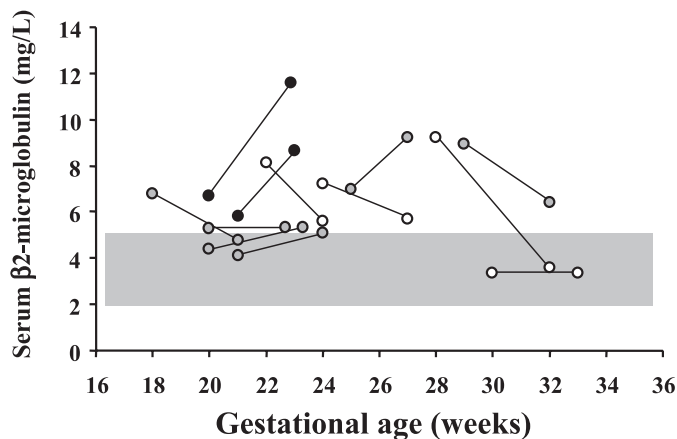
identified on ultrasound as being in situ. In 5 of these cases oligohydramnios recurred at 4 to 13 weeks after shunting, while in the remainder amniotic fluid volume was normal until delivery. All women but 1 delivered at 36 weeks or later (8 to 19 weeks after shunting), and the shunts were in place at delivery. The 10 neonates survived to 3 months to 5 years of followup but only 4 patients had normal renal function at the latest evaluation. The remaining 6 patients had varying degrees of renal failure and 1 underwent transplantation at age 2 years. Therefore, the incidence of renal dysplasia/failure was 67% (8 of 12 patients), and excluding the 2 pregnancies that were terminated, survival rate was 100% (10 of 10).

Table 1 summarizes the prenatal findings and outcomes of the 12 cases. Urinary Na^+ was below the threshold of 100 mEq/l in 9 fetuses, and urinary $\beta 2$ -microglobulin was below the threshold of 13 mg/l in 7. Serum $\beta 2$ -microglobulin was normal before shunting in only 3 fetuses. The figure displays the changes in serum $\beta 2$ -microglobulin at 2 to 4 weeks after shunting. Compared to baseline values, serum $\beta 2$ -microglobulin decreased in 5 fetuses, increased in 6 and remained stable in 1.

Table 2 outlines the prenatal findings in patients with normal renal function postnatally compared to those with renal dysplasia/failure. Although the numbers are too small to allow statistical analysis, no pre-shunting variable permitted accurate prediction of outcome. However, no fetus with persistent oligohydramnios and increasing serum $\beta 2$ -microglobulin after shunting had normal renal function. On the other hand, in 6 of the 8 cases with renal failure amniotic fluid volumes were normal for more than 4 weeks, and in 2 serum $\beta 2$ -microglobulin decreased after shunting.

TABLE 1. Prenatal findings and postnatal outcome in 12 fetuses with lower urinary tract obstruction treated with vesicoamniotic shunting

Case No.	Gestational Age at Shunting (wks)	Urinary Na^+ (mEq/l)	Urinary $\beta 2$ -Microglobulin (mg/l)	Serum $\beta 2$ -Microglobulin (mg/l)		Amniotic Fluid Vol After Shunting	Gestational Age at Delivery (wks)	Outcome
				Before Shunting	After Shunting			
1	20	121	15	6.7	11.6	Persistent oligohydramnios	23	Pregnancy terminated due to renal dysplasia
2	21	76	7	5.7	8.7	Persistent oligohydramnios	23	Pregnancy terminated due to renal dysplasia
3	22	110	29	8.1	5.6	Normal until delivery	39	Normal renal function at 5 yrs
4	20	72	10	5.4	5.7	Normal until 31 wks, oligohydramnios thereafter	38	Renal failure at 3 yrs, awaiting renal transplant
5	21	77	7	4.1	4.9	Normal until delivery	33	Renal failure at 3 yrs, awaiting renal transplant
6	20	93	4	4.4	5.3	Normal until 31 wks, oligohydramnios thereafter	36	Renal transplant at 2 yrs
7	25	75	—	7.0	9.2	Normal until 29 wks, oligohydramnios thereafter	36	Renal failure at 3 yrs, awaiting renal transplant
8	28	81	4	9.2	3.6	Normal until 34 wks, oligohydramnios thereafter	37	Normal renal function at 18 mos
9	30	53	3	3.6	3.6	Normal until delivery	38	Normal renal function at 18 mos
10	29	105	31	8.8	6.9	Normal until delivery	38	Renal failure at 1 yr
11	18	98	10	6.8	4.8	Normal until 31 wks, oligohydramnios thereafter	37	Renal failure at 4 mos
12	24	75	20	7.2	5.7	Normal until delivery	38	Normal renal function at 3 mos



Values of fetal serum β 2-microglobulin (mg/l) at samples taken before and after shunting. Black circles indicate fetuses with dysplastic kidneys at autopsy. Gray circles indicate patients with postnatal development of renal failure. White circles indicate patients with normal postnatal renal function.

DISCUSSION

Vesicoamniotic shunting is the principal option for prenatal treatment of obstructive uropathy. Suggested benefits, based on experimental observations, include prevention of pulmonary hypoplasia and renal dysplasia. One systematic review and meta-analysis of lower urinary tract obstruction that included 342 fetuses revealed that prenatal bladder drainage (vesicocentesis, vesicoamniotic shunt or open fetal bladder surgery) improved perinatal survival compared to the nondrainage group (odds ratio 2.5, 95% confidence intervals 1.1 to 5.9, $p < 0.03$).¹⁰ This improved survival was mainly observed in cases in which ultrasound and urinary analyses suggested a poor prognosis. However, the long-term outcome for most survivors is poor due to the common progression to end stage renal failure.

Once associated malformations and chromosomal abnormalities have been ruled out, assessment of renal function is essential in the decision process when considering whether to offer prenatal treatment.⁴ This evaluation is generally accomplished by analysis of fetal urinary electrolytes and β 2-microglobulin, which are increased in fetuses with renal dysplasia. However, there is no general agreement on which is the best test or combination of tests to predict postnatal renal function.

There are also intrinsic limitations to this approach. At best, urinary components reflect tubular function rather than glomerular filtration rate. Additionally, although urinalysis performed serially has been shown to be more predictive than a single assessment,¹¹ successful placement of a shunt prevents further samplings. Therefore, monitoring of the effect of treatment on renal function cannot be performed by urinalysis. Failure of reaccumulation of amniotic fluid after shunting likely reflects severe renal damage. However, in those cases in which amniotic fluid volume improves it is undetermined whether shunting has an impact on the evolution of renal damage.

Fetal blood sampling probably poses greater risks than urine sampling but it allows measurement of serum β 2-microglobulin at the same time as rapid karyotyping. β 2-microglobulin is an index of glomerular filtration rate, and its levels do not change with advancing gestational age. The

assay of β 2-microglobulin in fetal serum has been demonstrated to be predictive of renal damage in fetuses with urinary tract abnormalities.^{7,8,12} Changes in serum β 2-microglobulin levels might reflect the evolution of renal function with advancing gestation following intrauterine shunting.

All 12 fetuses in this study had proved posterior urethral valves, all had oligohydramnios at the time of shunting and 4 were in the late second trimester. Contrary to most series, there were no complications of shunting, and with the exception of the 2 pregnancies that were terminated the interval from prenatal intervention to delivery ranged from 8 to 19 weeks. The resulting survival rate was 100%, and there were no deaths due to lung hypoplasia, probably because in all pregnancies intended to continue the amniotic fluid volume was normal following shunt placement for a minimum of 4 weeks. However, only 4 infants were without renal impairment at the last followup.

β 2-microglobulin was increased in 9 of the 12 fetuses that underwent sampling at the time of shunting. Although urinary sodium was higher than the accepted threshold in only 3 fetuses, this finding suggests that some degree of renal damage had already occurred. Fetal blood sampling was repeated at an arbitrarily chosen interval of 2 to 4 weeks after shunting. The levels of serum β 2-microglobulin increased in 6 fetuses, of which 2 had persistent oligohydramnios and renal dysplasia at autopsy following pregnancy termination. Renal failure developed in the remaining 4 patients postnatally.

The evidence of renal dysplasia and severe impairment of renal function in these cases suggests that renal damage due to early urinary tract obstruction may progress despite relief of standing pressure in the urinary tract following the placement of a shunt. However, in 5 fetuses the levels of serum β 2-microglobulin decreased following shunting. Three of these patients have normal renal function, while renal failure has developed in the other 2. Therefore, amelioration of renal function in utero due to decompression of the urinary tract does not rule out that damage has occurred to an extent that cannot entirely be reversed. Within these limitations this 2-step approach to evaluating fetuses with lower uri-

TABLE 2. Normal renal function or renal dysplasia/failure in relation to prenatal variables

	Normal Renal Function	Renal Dysplasia/ Renal Failure
Gestational age at shunting (wks):		
Less than 24	2	6
24 or More	2	2
Urinary Na ⁺ (mEq/l):		
100 or Greater	1	2
Less than 100	3	6
Urinary β 2-microglobulin (mg/l):		
13 or Greater	2	2
Less than 13	2	5
Serum β 2-microglobulin (mg/l):		
4.9 or Greater	3	6
Less than 4.9	1	2
Persistent oligohydramnios after shunting	0	2
Normal amniotic fluid vol after shunting greater than 4 wks	4	6
Change in serum β 2-microglobulin (mg/l) after shunting:		
Increased	0	6
None	1	0
Decreased	3	2

nary tract obstruction has the advantage of allowing counseling of women who choose to undergo intrauterine intervention regarding the likelihood that shunting has or has not been of benefit to fetal renal function.

CONCLUSIONS

The combination of increasing serum β 2-microglobulin and persistent oligohydramnios following intrauterine shunting of fetuses with lower urinary tract obstruction is associated with a poor prognosis. On the other hand, reaccumulation of amniotic fluid and improvement of glomerular filtration rate do not rule out development of renal failure postnatally.

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