

Can We Predict Severity of Renal Dysplasia Antenatally ?

BC Nephrology Days 2007
Vancouver, BC

Peter Trnka, MD, FRACP
Pediatric Nephrologist
BC Children's Hospital

Outline

- Importance of fetal renal dysplasia to pediatric nephrologist
- Diagnosis, treatment, and outcomes of treatment of obstructive fetal renal dysplasia
- Pathophysiology of obstructive fetal renal dysplasia
- Biomarkers of fetal renal dysplasia
- Study

Causes of CKD in Childhood

	All Registered Patients		Patients Reaching ESRD	
	No	%	No	%
Hypodysplasia				
with identified uropathy	522	44	71	27
without urinary tract malformation	167	14	33	13
Polycystic kidney disease	60	5	9	3
Cortical necrosis (perinatal)	49	4	8	3
Hereditary nephropathies	45	4	13	5
Neurogenic bladder	44	4	8	3
Hemolytic uremic syndrome	43	4	9	3
Nephronophthisis	41	3	21	8

Andrissino G *et al.*, Pediatrics, 2003

Causes of CKD in Childhood

	All Registered Patients		Patients Reaching ESRD	
	No	%	No	%
Hypodysplasia				
with identified uropathy	522	44	71	27
without urinary tract malformation	167	14	33	13
Polycystic kidney disease	60	5	9	3
Cortical necrosis (perinatal)	49	4	8	3
Hereditary nephropathies	45	4	13	5
Neurogenic bladder	44	4	8	3
Hemolytic uremic syndrome	43	4	9	3
Nephronophthisis	41	3	21	8

Andrissino G *et al.*, Pediatrics, 2003

Urinary Tract Malformations Associated with Hypodysplasia in Children with CKD

Urinary Malformation	No	%
Vesicoureteral reflux	309	59
Posterior urethral valves	124	24
Ureteropelvic junction stenosis	19	4
Obstructive megaureter	18	4
Urethral hypoplasia/atresia	12	2
Ureterocele	9	2
Duplication of collection system	8	2

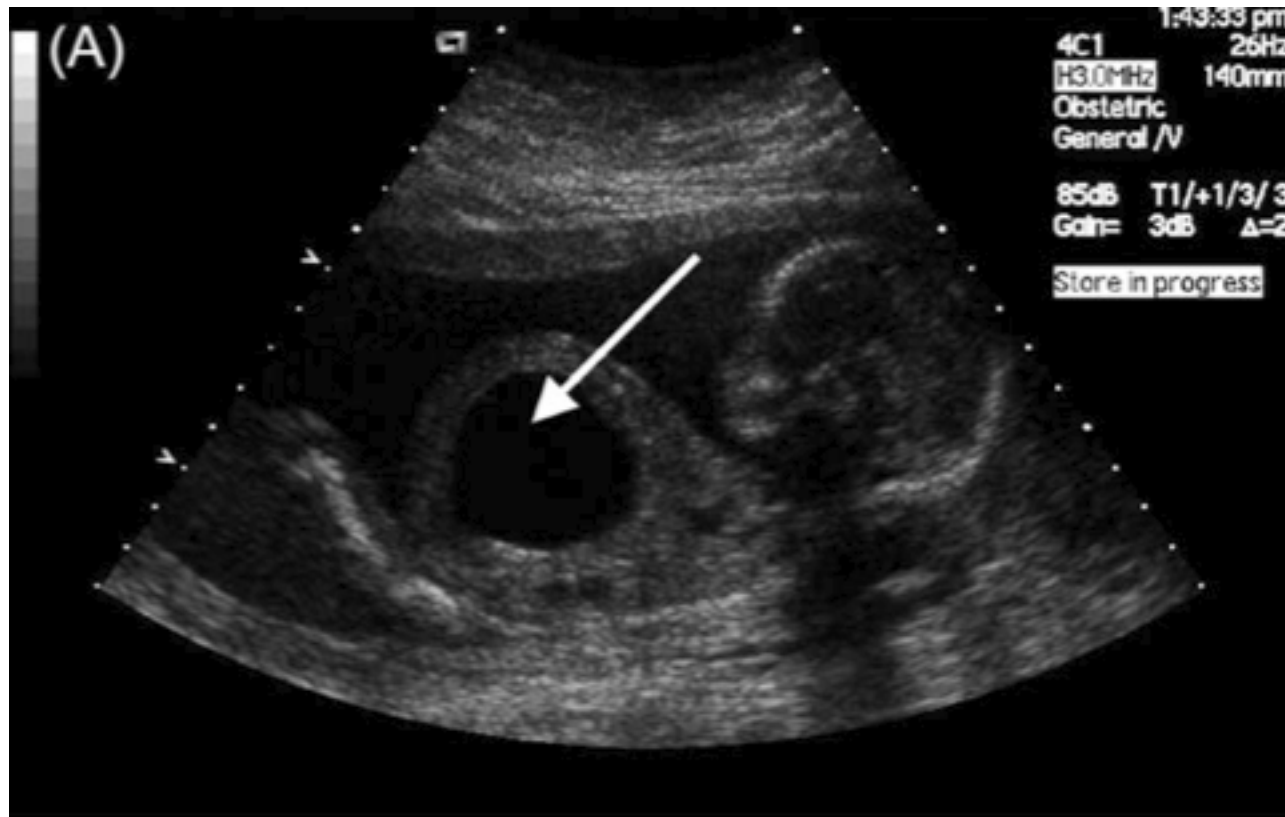
Andrissino G *et al.*, Pediatrics, 2003

Urinary Tract Malformations Associated with Hypodysplasia in Children with CKD

Urinary Malformation	No	%
Vesicoureteral reflux	309	59
Posterior urethral valves	124	24
Ureteropelvic junction stenosis	19	4
Obstructive megaureter	18	4
Urethral hypoplasia/atresia	12	2
Ureterocele	9	2
Duplication of collection system	8	2

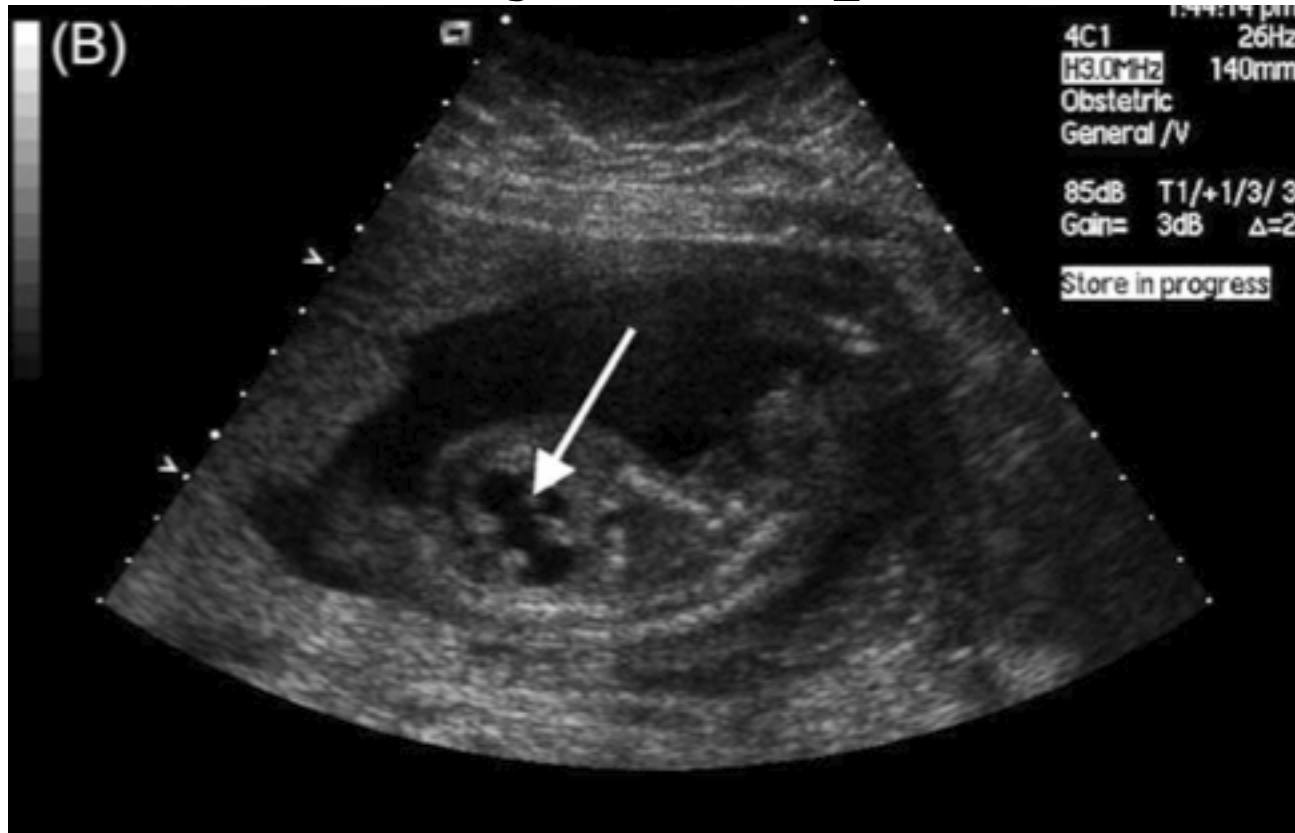
Andrissino G *et al.*, Pediatrics, 2003

Enlarged Fetal Bladder



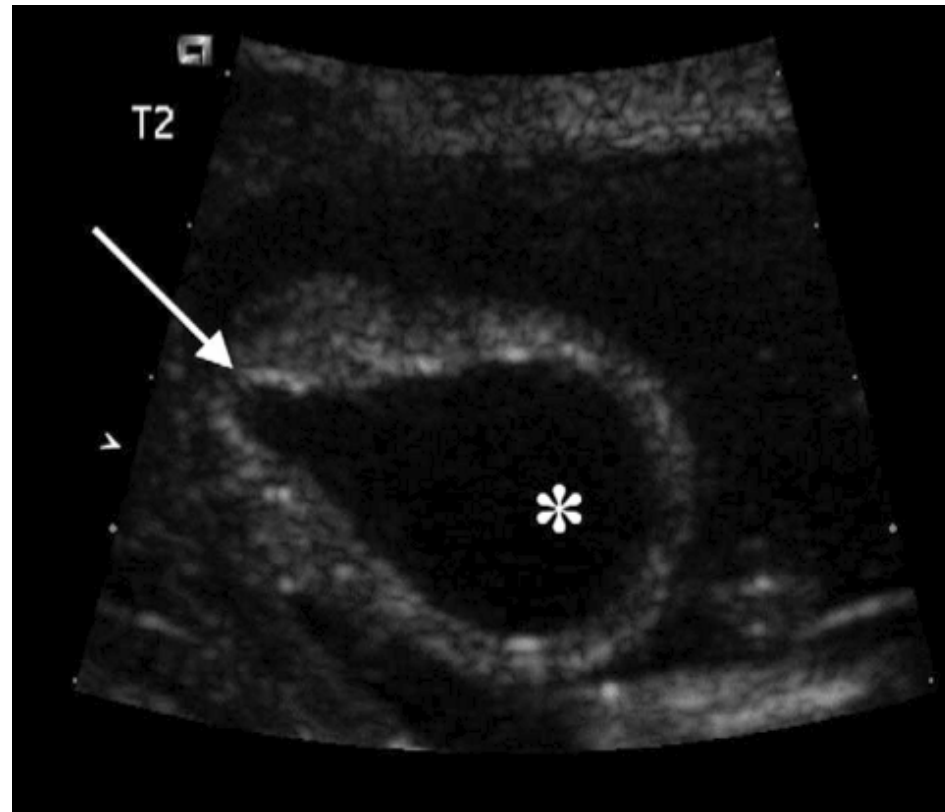
Vanderheyden T *et al.*, Seminars in Neonatology, 2003

Fetal Hydronephrosis



Vanderheyden T *et al.*, Seminars in Neonatology, 2003

Dilated Posterior Urethra



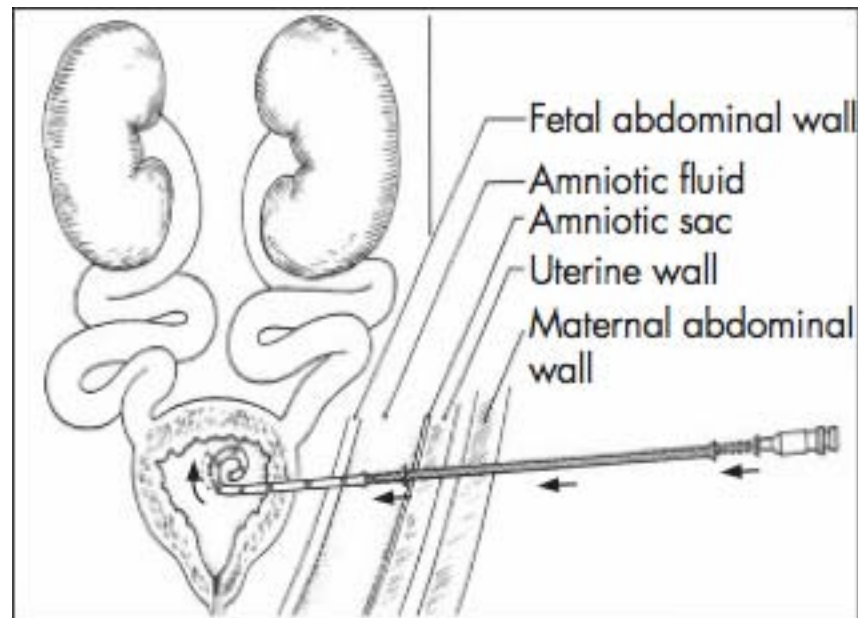
Vanderheyden T *et al.*, Seminars in Neonatology, 2003

“Bright” Enlarged Kidneys



Winyard P *et al.*, Prenatal Diagnosis, 2001

In Utero Therapy for LUTO Vesico-Amniotic Shunting



Morris RK *et al.*, Arch.Dis.Child.Fetal Neonatal Ed., 2007

Outcome Studies of Prenatal Intervention

	<i>n</i>	<i>Survivors</i>	<i>Normal Function</i>	<i>Pulmonary Hypoplasia</i>	<i>Intrauterine Death</i>	<i>TOP</i>
<i>Freedman et al. (1996, 1999)</i>	28	17	12	6	3	1
<i>Lipitz et al. (1993)</i>	14	6	0	5	1	2
<i>Crombleholme et al. (1988, 1990)</i>	19	12	7	4	1	3
<i>Manning (1991)</i>	87	35	16	28	4	13
<i>Elder et al. (1987)</i>	21	9	1	4	0	3
Total (%)	169	79/169 (47)	36/60 (60)	47/76 (62)	9	22

Agarwal SK *et al.*, Prenatal Diagnosis, 2001

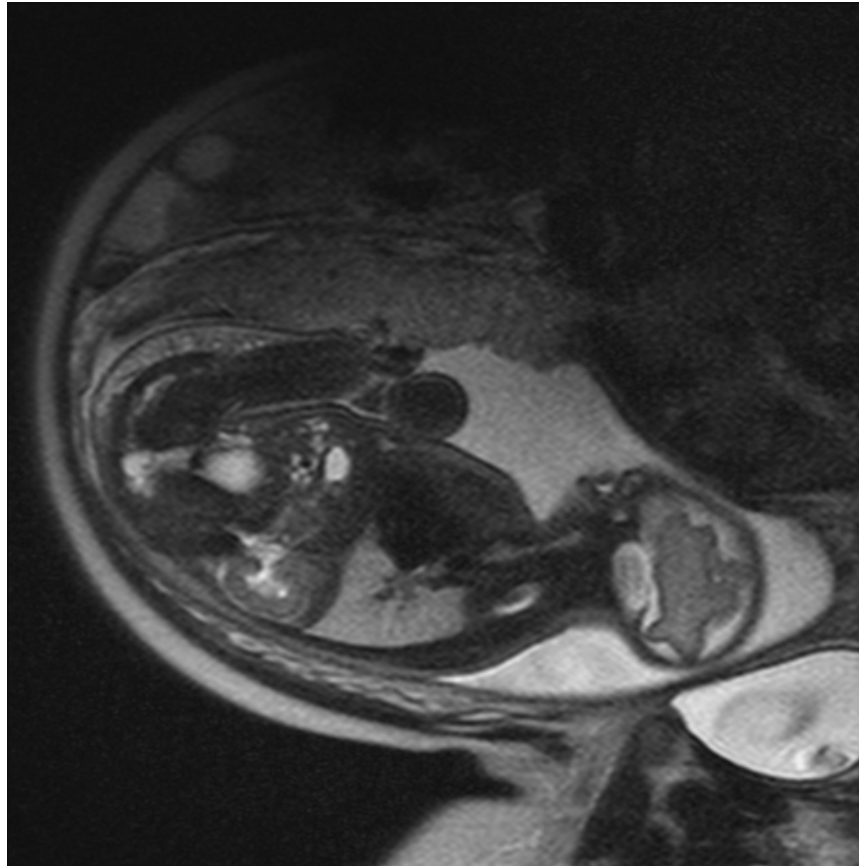
Accuracy of Antenatal Ultrasound (56 Cases with LUTO)

Sensitivity 10/18 = 56%
Specificity 10/17 = 59%
PPV 10/17 = 59%
NPV 10/18 = 56%

Pregnancies terminated or early NND	42
Fetal autopsy	36 (86%)
Bilateral renal dysplasia	10
Normal renal parenchyma	11
Dysplasia not ascertained	15
Dysplasia/CKD on follow-up	18
Echogenic or cystic renal parenchyma on scan	10
No dysplasia/normal renal function on follow-up	17
Normal renal scan	10

Anumba DO *et al.*; Prenatal Diagnosis, 2005

Antenatal MRI

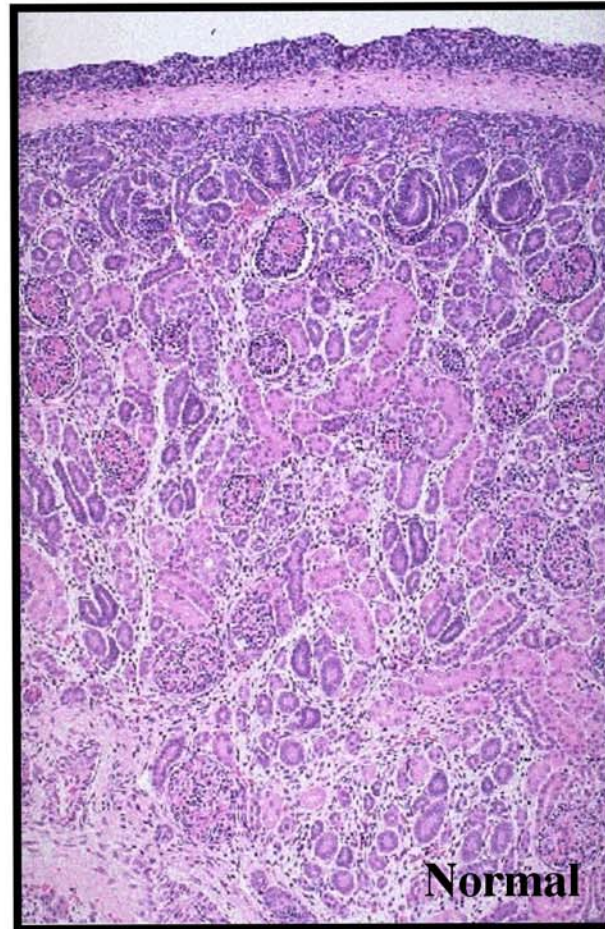
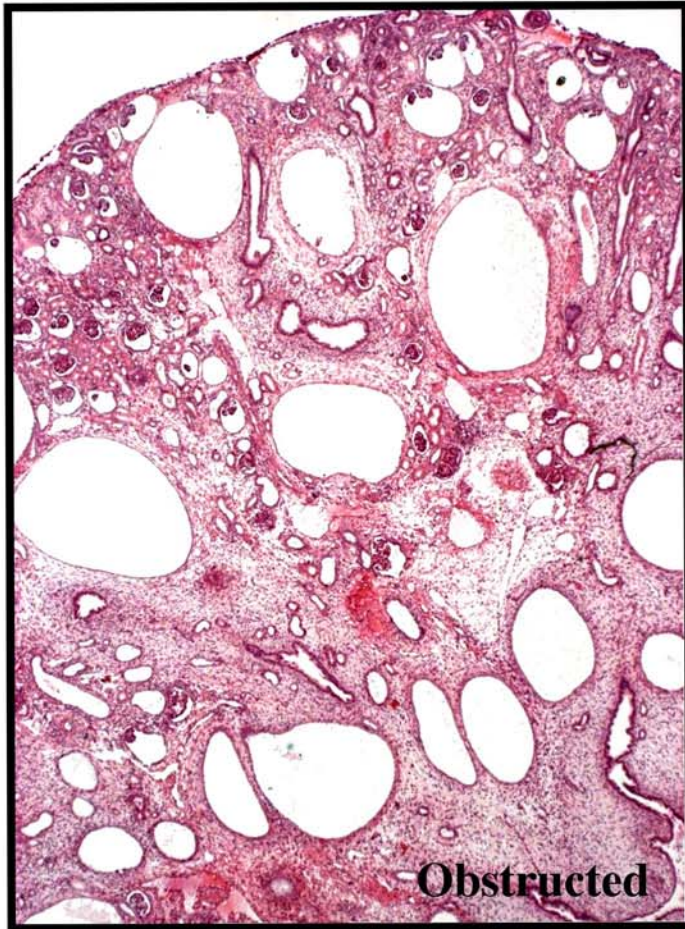


Antenatal MRI



Yu-Peng L *et al.*, Pediatric Radiology, 2007

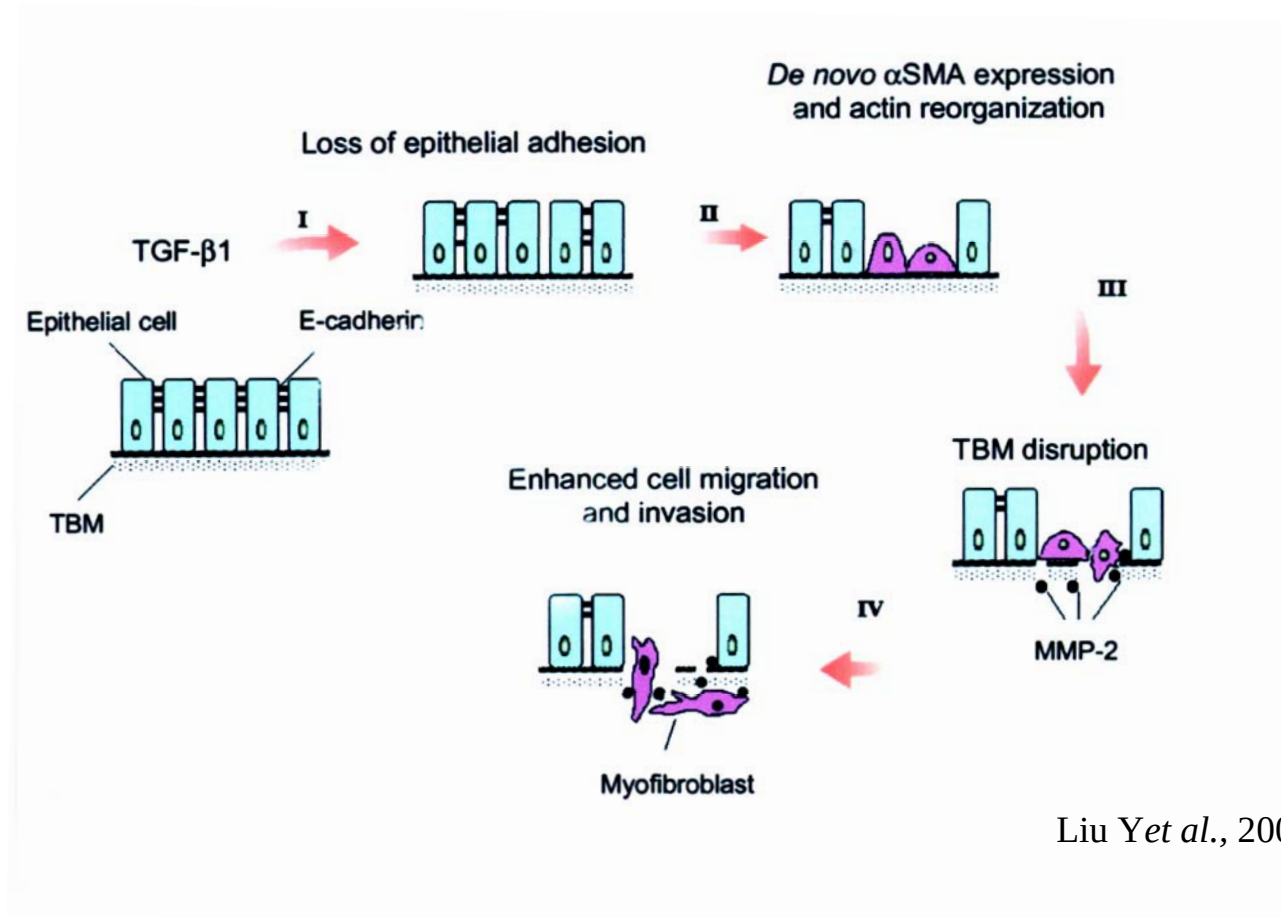
Fetal Renal Biopsy



Fetal Urinalysis and Blood Sampling

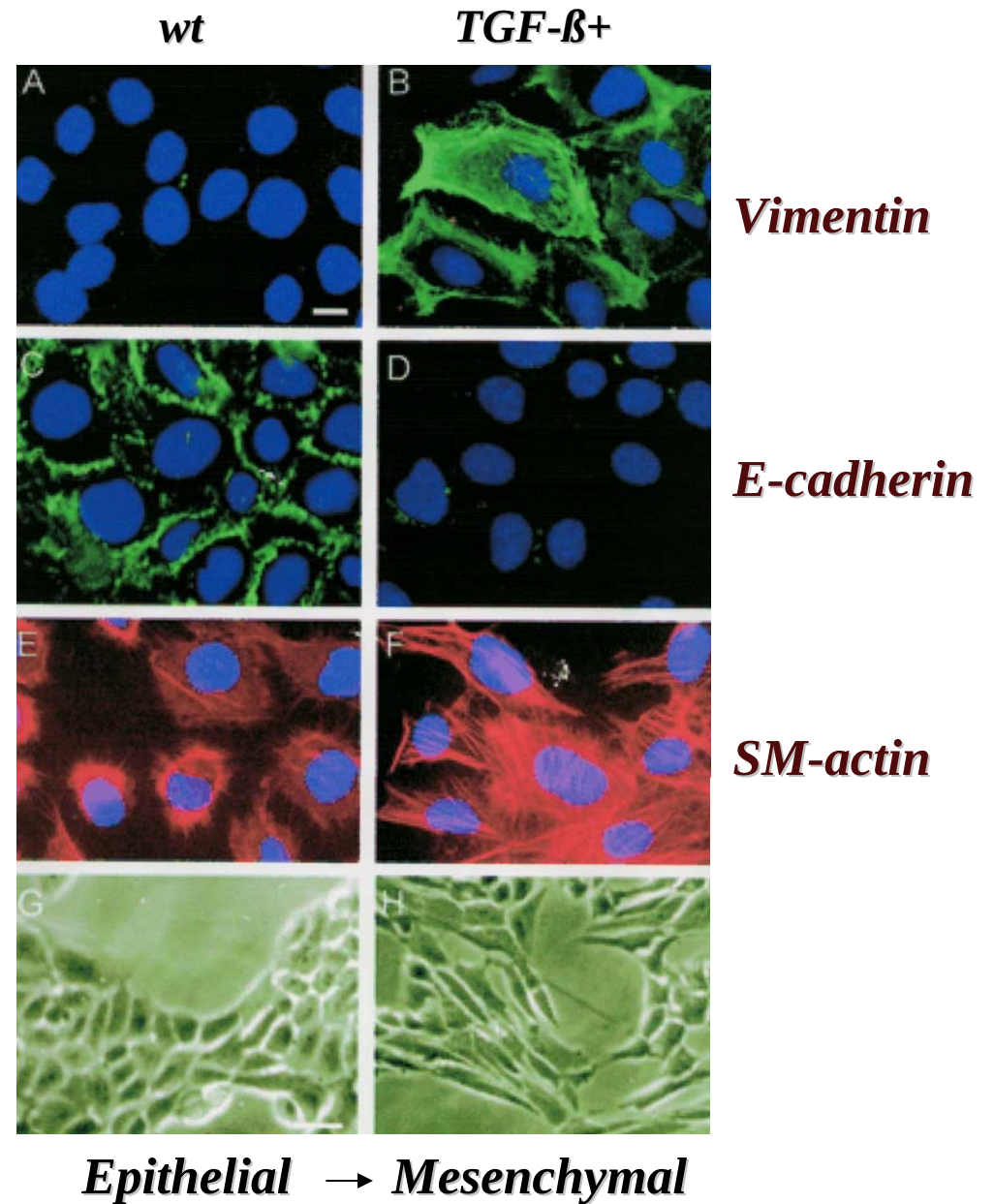
Predictor	Sensitivity	Specificity	Reference
Increased urinary sodium	50 - 80%	60 - 80%	Nicolini <i>et al.</i> (1992) Muller <i>et al.</i> (1996)
Increased urinary calcium	70 - 100%	60 - 80%	Nicolini <i>et al.</i> (1992) Muller <i>et al.</i> (1996)
Increased urinary β_2 -microglobulin	80%	83%	Lipitz <i>et al.</i> (1993) Muller <i>et al.</i> (1993) Muller <i>et al.</i> (1996)
Increased serum β_2 -microglobulin	80%	99%	Berry <i>et al.</i> (1995) Tassis <i>et al.</i> (1997)

Epithelial-Mesenchymal-Myocyte Transformation

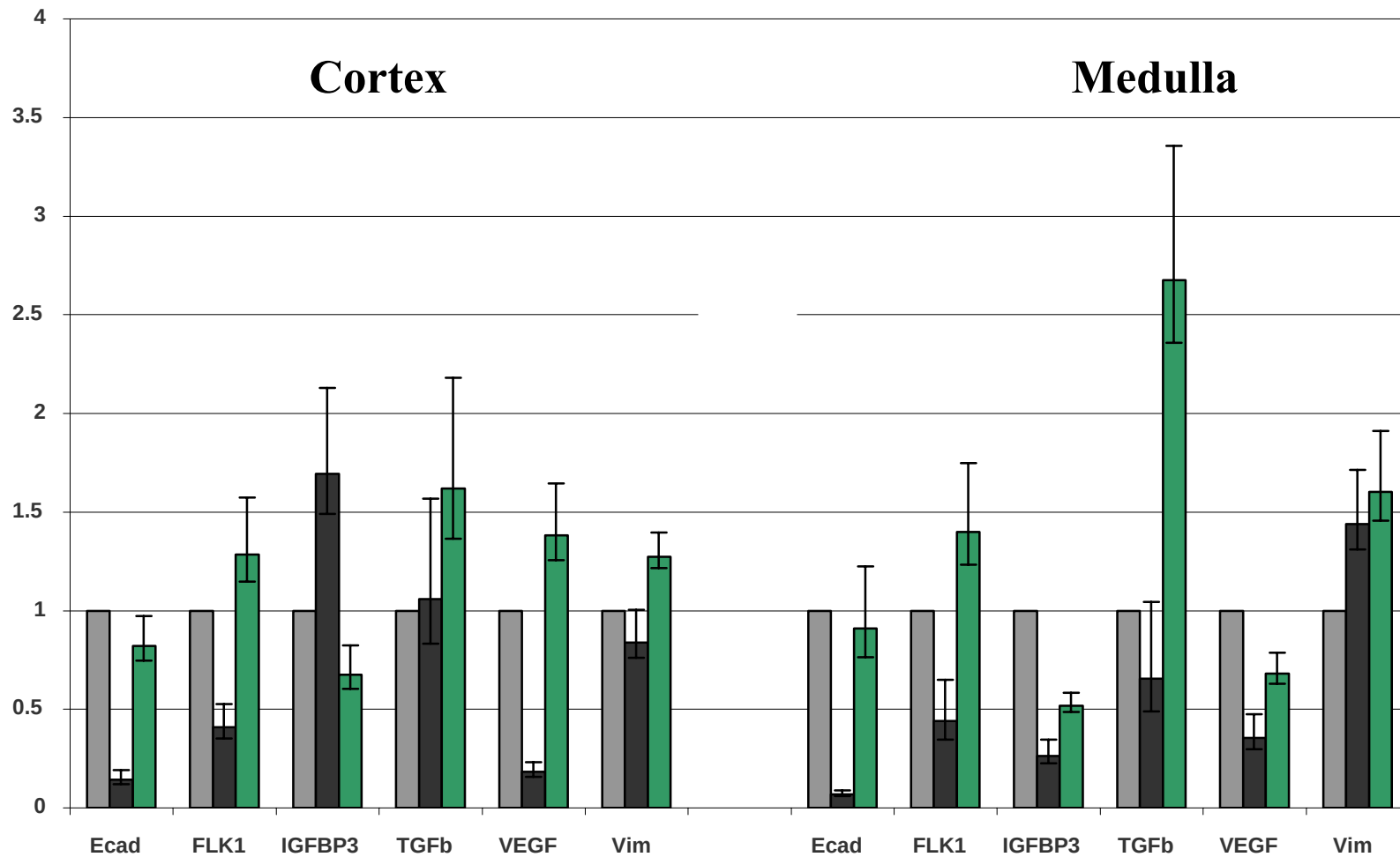


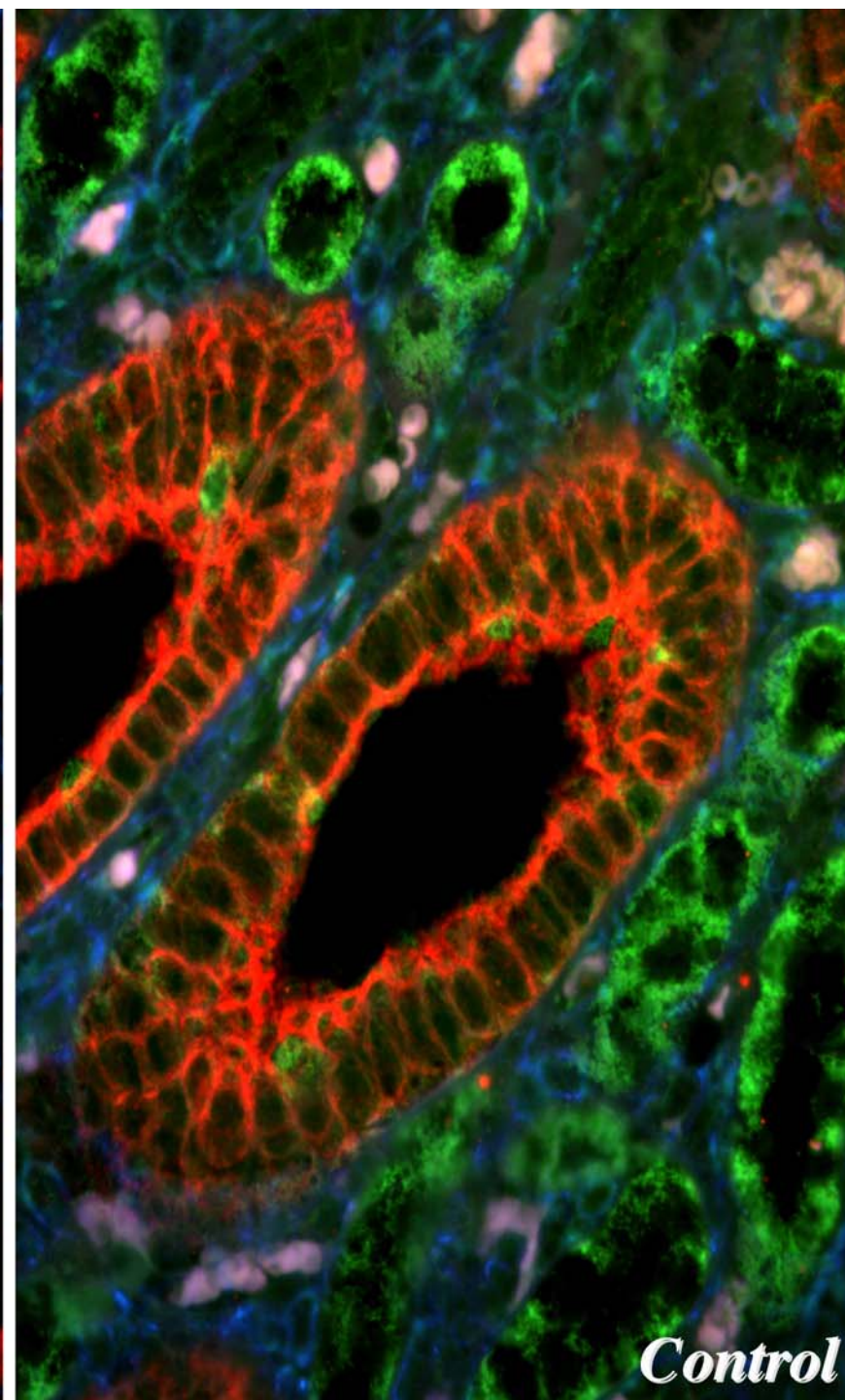
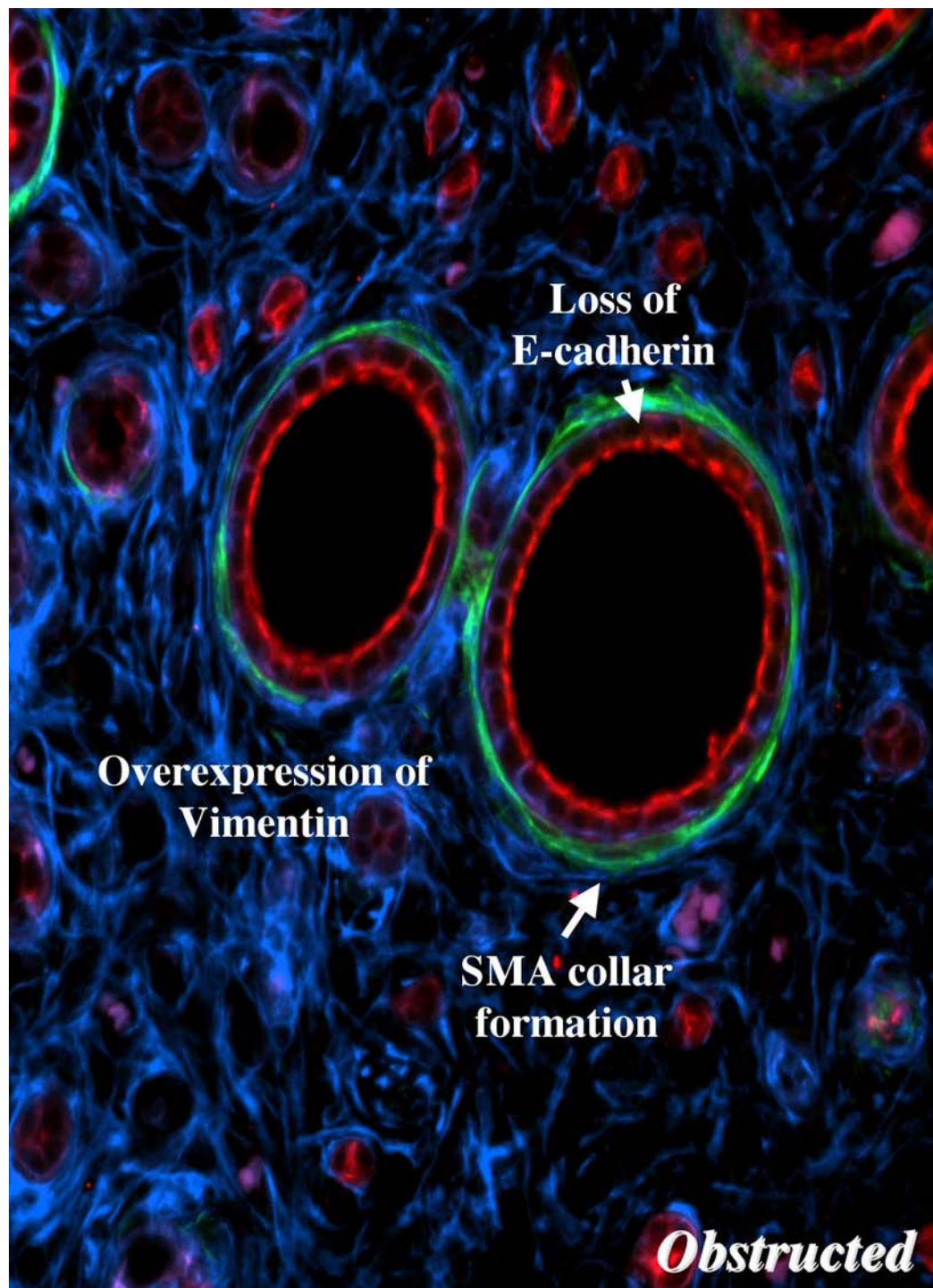
Epithelial-Mesenchymal Transformation In Fibrosis

Liu Y *et al.*, 2003



Biomarkers of Renal Dysplasia





Study

Fetal Urinary Transforming Growth Factor- β 1 Levels Predict the Severity of Renal Dysplasia

Peter Trnka, Doug Matsell - Division of Nephrology

Peter von Dadelszen - Maternal-Fetal Medicine

Doug Jamieson - Radiology

Aim of the Study

- To evaluate the utility of amniotic fluid, antenatal fetal urine, and postnatal urine concentrations of TGF- β 1 as a predictor of severity of postnatal renal impairment due to fetal renal dysplasia
- To develop an outcome prediction model based on imaging and functional renal tests to predict renal impairment at one year of age

Timing of appointments and investigations

ANTENATAL PERIOD

CASES
+
CONTROLS

RENAL
ULTRASOUND

AMNIOTIC
FLUID VOLUME

amniotic fluid TGF- β 1
fetal urine TGF- β 1
fetal urine electrolytes,
Ca, osmolality,
 β_2 -microglobulin

Timing of appointments and investigations

ANTENATAL PERIOD	MONTH 1
CASES + CONTROLS	CASES + CONTROLS
RENAL ULTRASOUND AMNIOTIC FLUID VOLUME amniotic fluid TGF- β 1 fetal urine TGF- β 1 fetal urine electrolytes, Ca, osmolality, β_2 -microglobulin	RENAL ULTRASOUND SERUM CREATININE urine TGF- β 1 + proteinuria

Timing of appointments and investigations

ANTENATAL PERIOD	MONTH 1	MONTHS 3 & 6
CASES + CONTROLS	CASES + CONTROLS	CASES
RENAL ULTRASOUND	RENAL ULTRASOUND	RENAL ULTRASOUND
AMNIOTIC FLUID VOLUME	SERUM CREATININE	SERUM CREATININE
amniotic fluid TGF- β 1 fetal urine TGF- β 1 fetal urine electrolytes, Ca, osmolality, β_2 -microglobulin	urine TGF- β 1 + proteinuria	urine TGF- β 1 + proteinuria

Timing of appointments and investigations

ANTENATAL PERIOD	MONTH 1	MONTHS 3 & 6	MONTH 12
CASES + CONTROLS	CASES + CONTROLS	CASES	CASES + CONTROLS
RENAL ULTRASOUND	RENAL ULTRASOUND	RENAL ULTRASOUND	RENAL ULTRASOUND*
AMNIOTIC FLUID VOLUME	SERUM CREATININE	SERUM CREATININE	SERUM CREATININE
amniotic fluid TGF- β 1 fetal urine TGF- β 1 fetal urine electrolytes, Ca, osmolality, β_2 -microglobulin	urine TGF- β 1 + proteinuria	urine TGF- β 1 + proteinuria	urine TGF- β 1 + proteinuria
			NUCLEAR GFR* RENAL MRI*

* - cases only

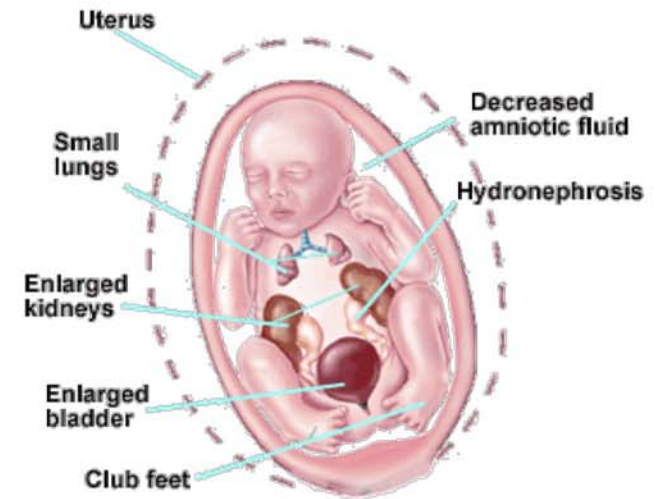
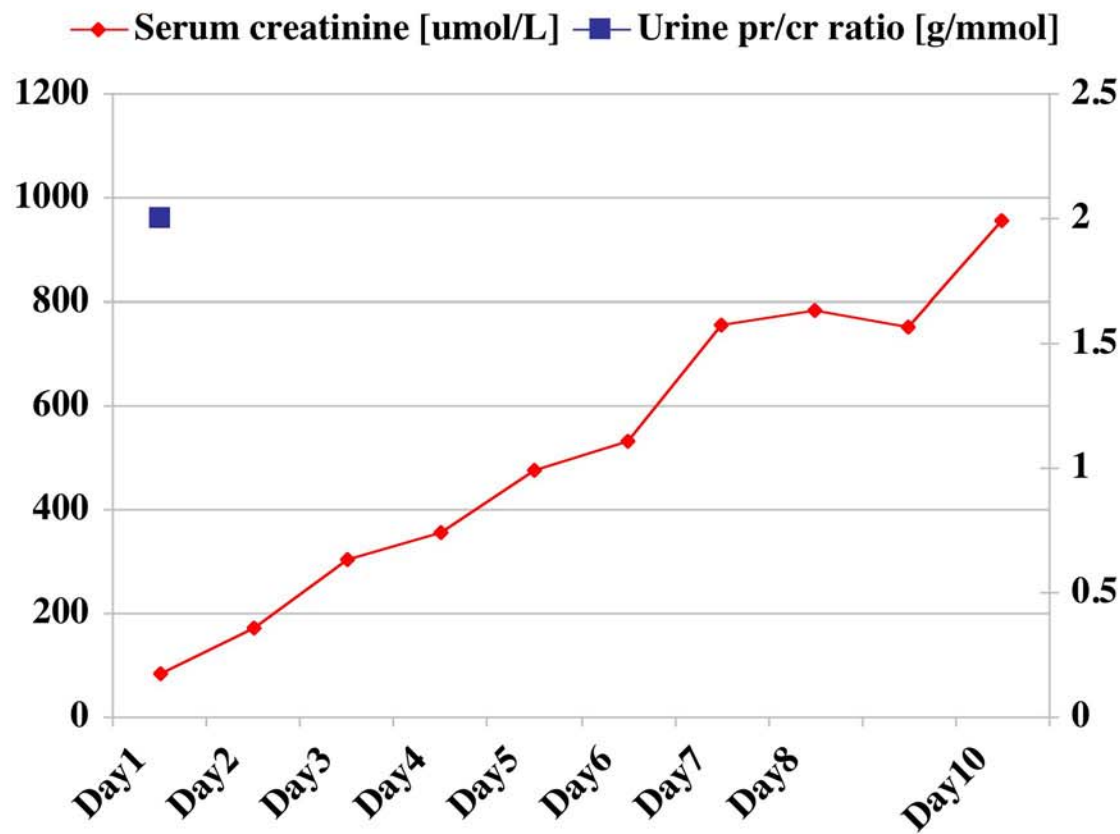
Proposed Scoring System for Severity of Renal Dysplasia

Points	0	1
<i>Renal ultrasound</i>		
Echogenicity of affected kidney	Normal	Increased
Cysts in affected kidney	Absent	Present
Cortico-medullary differentiation of affected kidney	Present	Absent
Renal growth of affected kidney over time	Normal	Absent
<i>Renal function</i>		
Oligohydramnios on antenatal ultrasound	Absent	Present
Age related serum creatinine level	Normal	Elevated
Proteinuria – protein/creatinine ratio	< 50	≥ 50

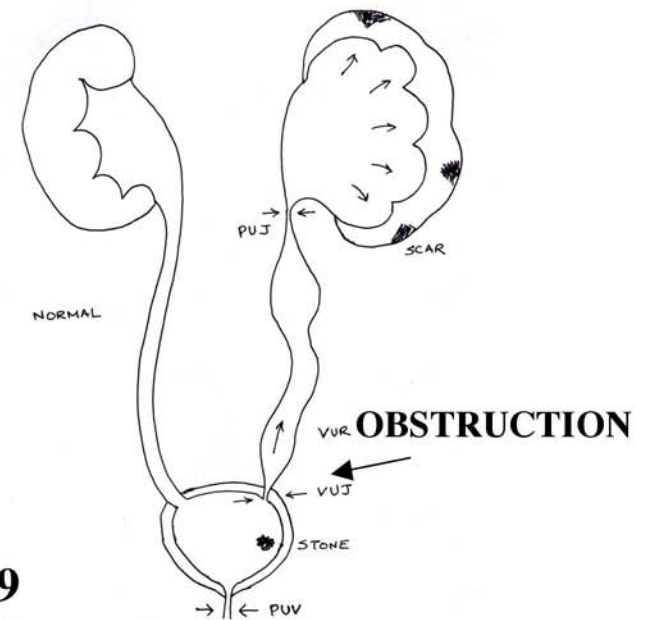
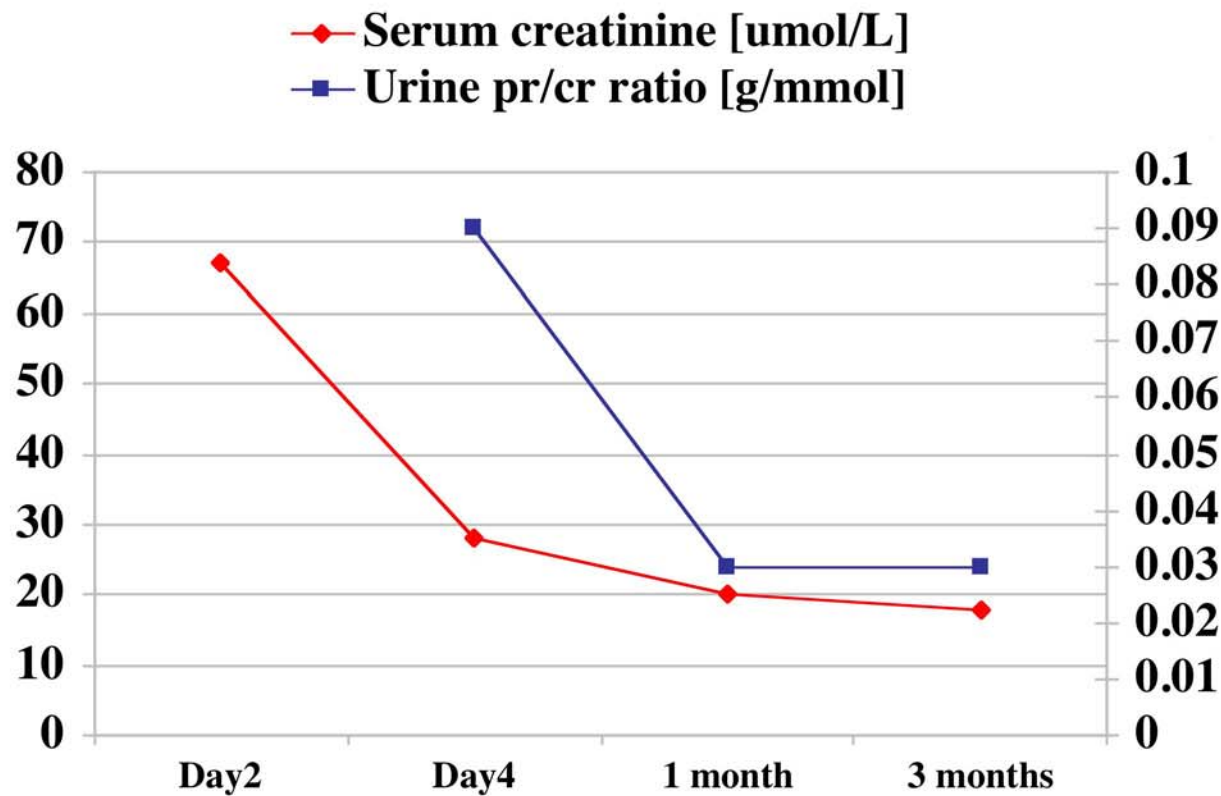
Controls at 1 month of age

- $n = 18$ (12 female)
- normal antenatal and postnatal ultrasounds
- serum creatinine 19 $\mu\text{mol/L}$ ($\text{SD} \pm 2$)
- protein/creatinine ratio 0.04 g/mmol ($\text{SD} \pm 0.04$)

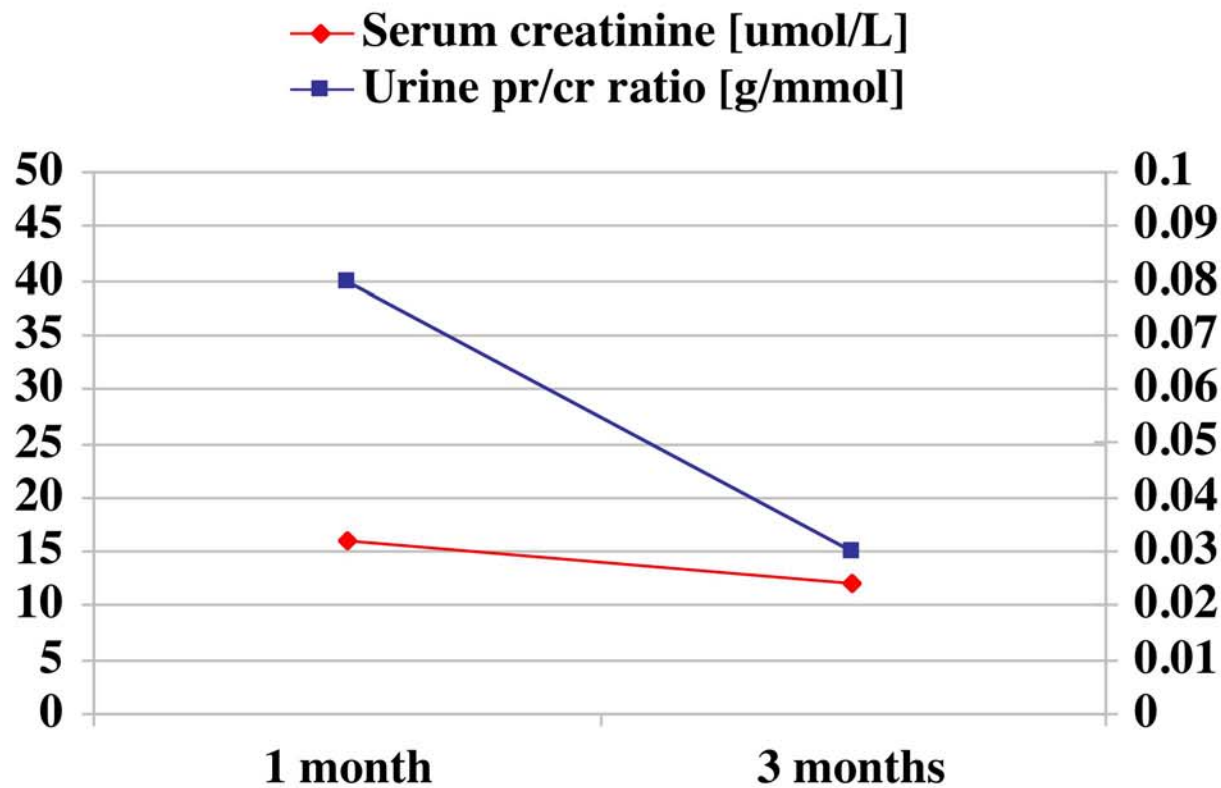
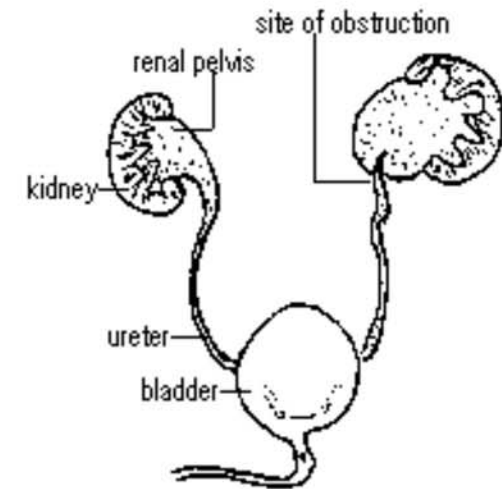
Case 1 (PUV)



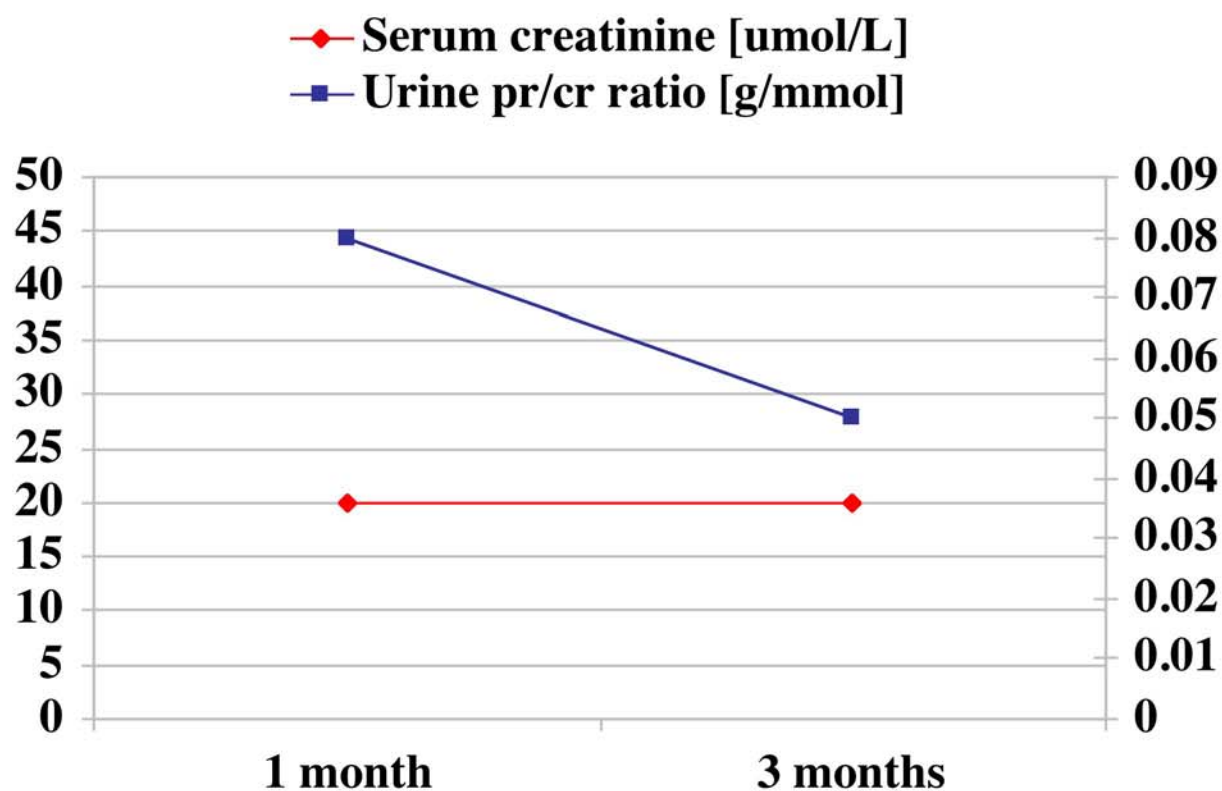
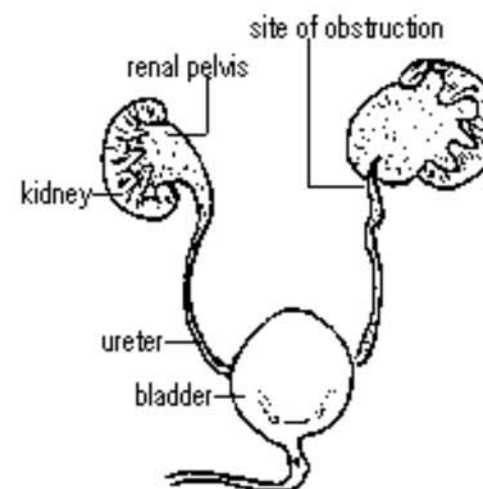
Case 2 (VUJO)



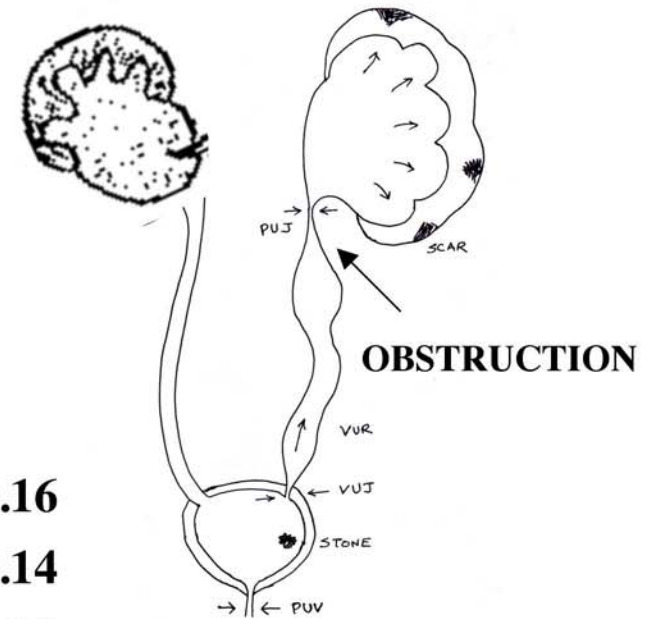
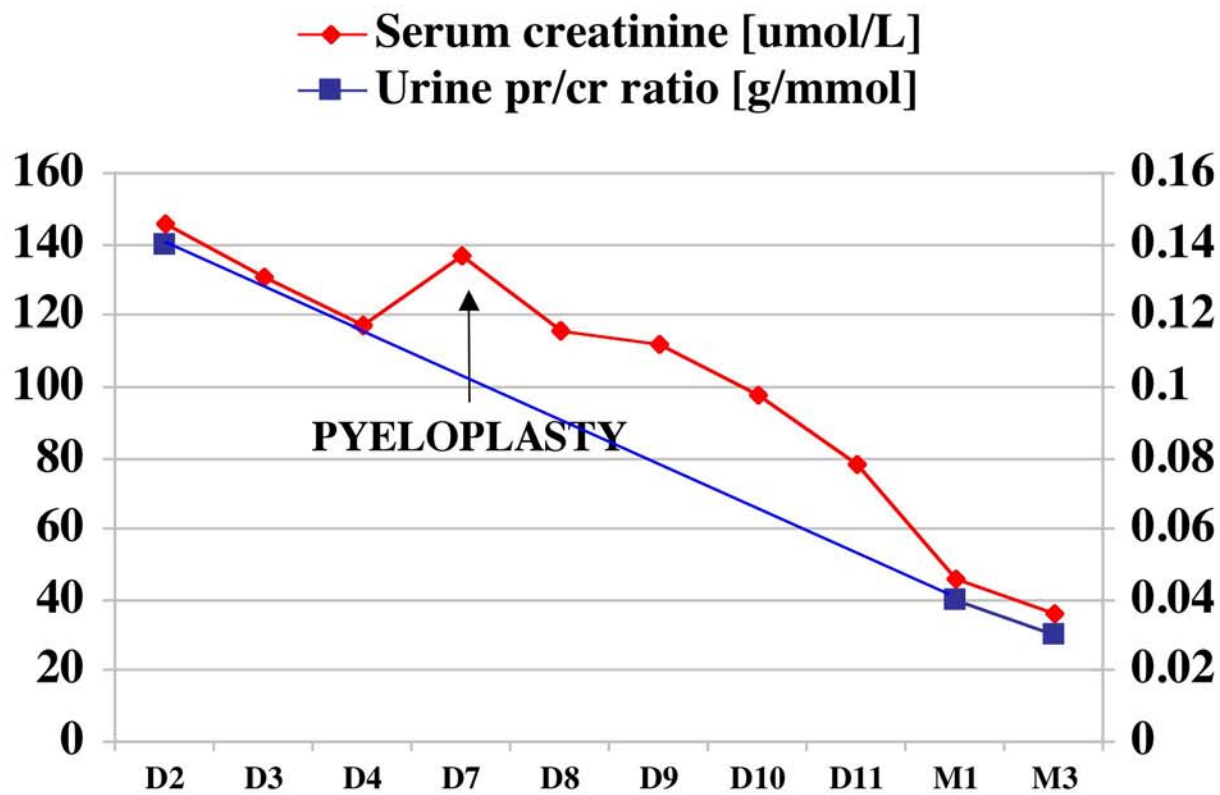
Case 3 (MCDK)



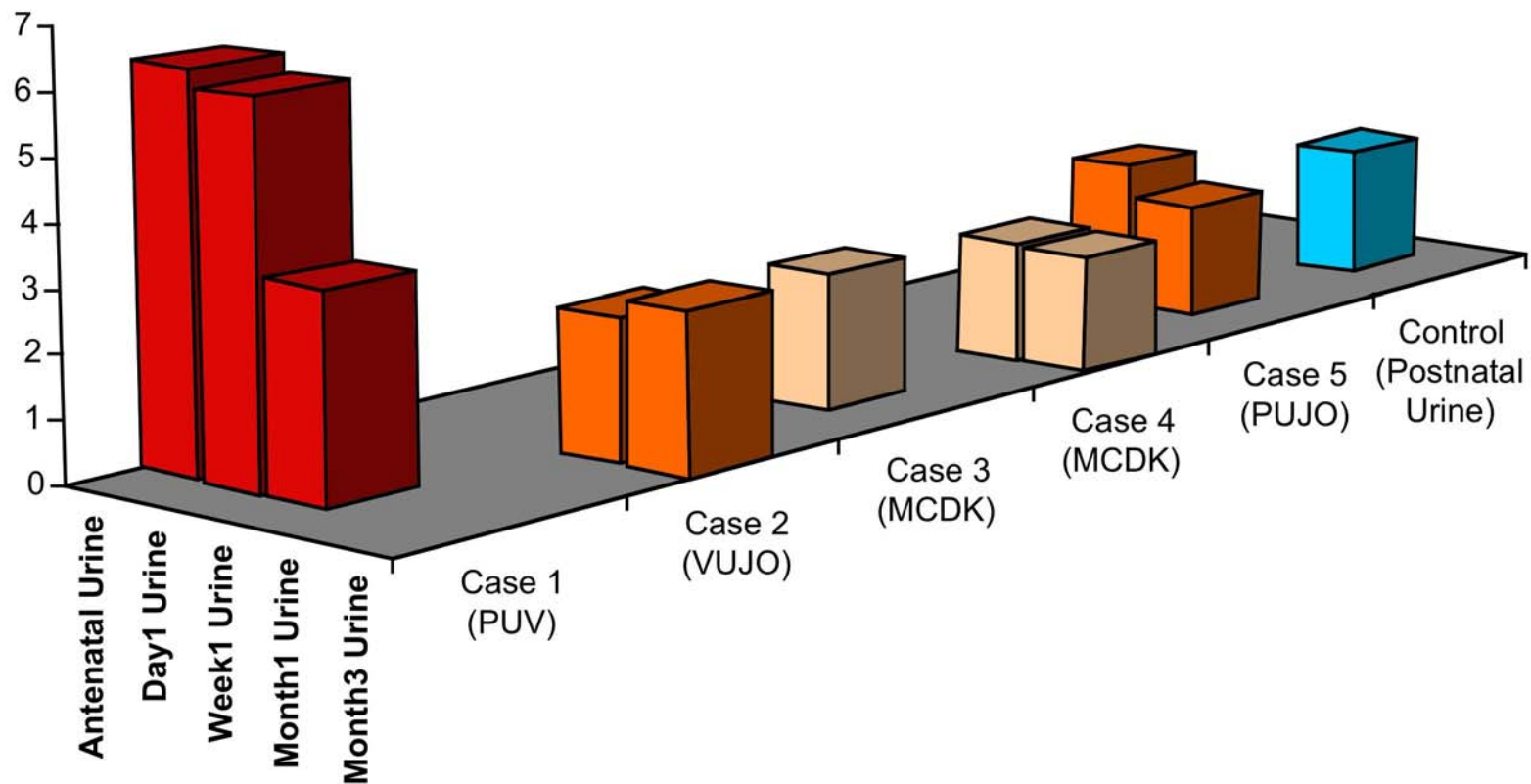
Case 4 (MCDK)



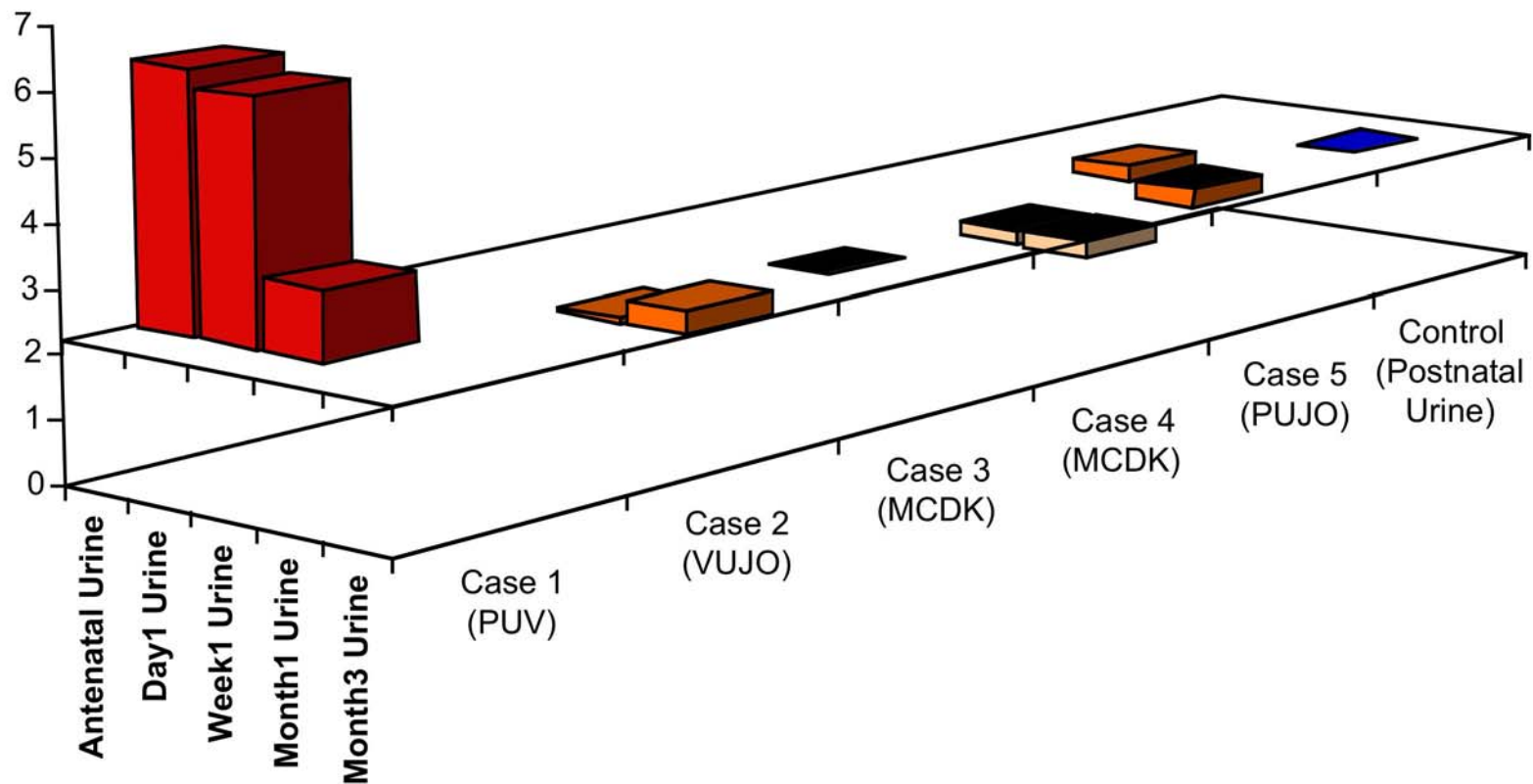
Case 5 (MCDK+PUJO)



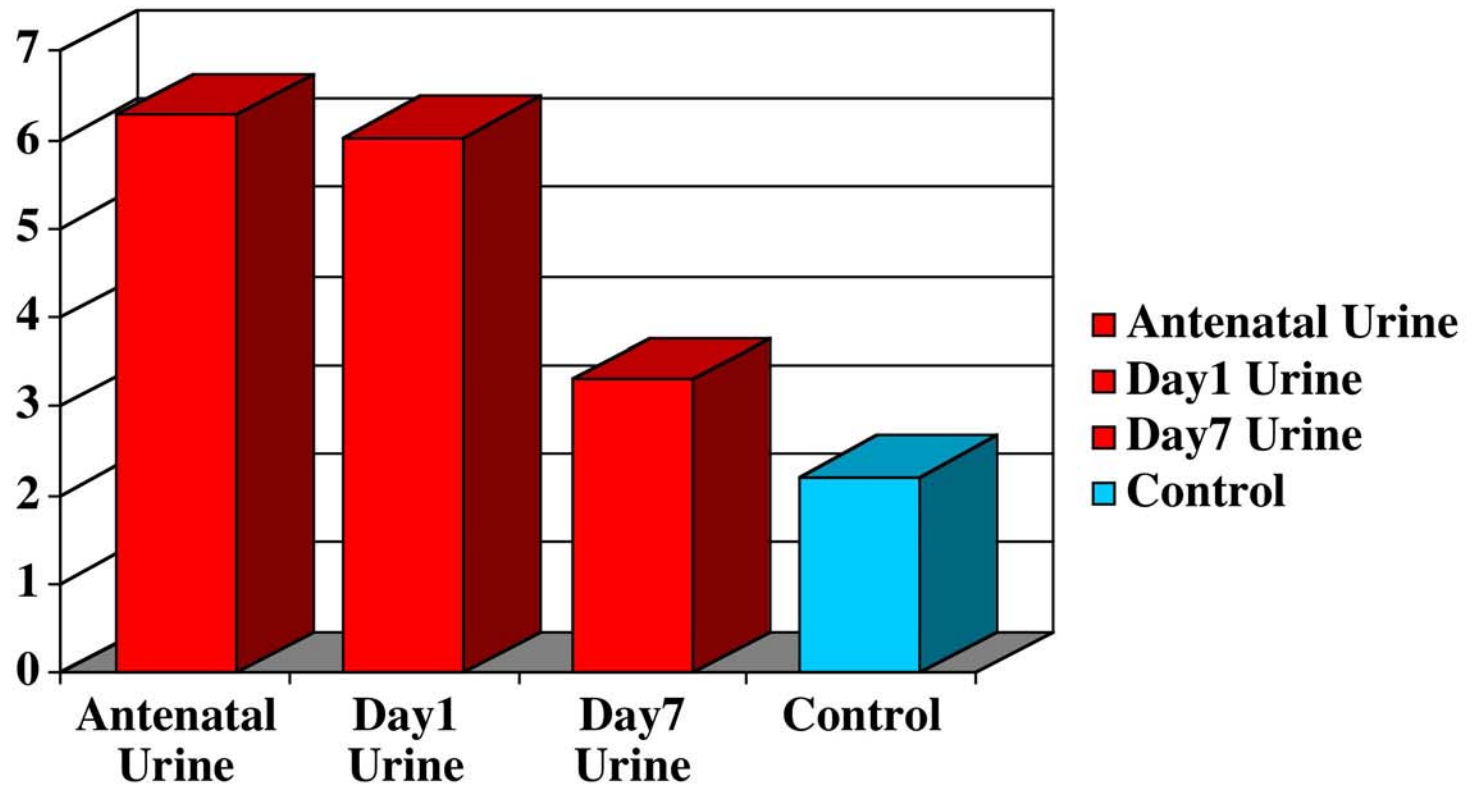
Urine TGF- β 1 Levels

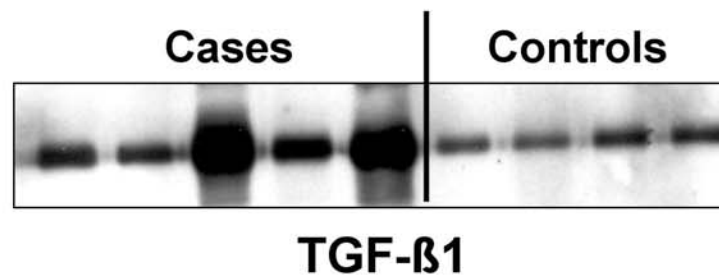
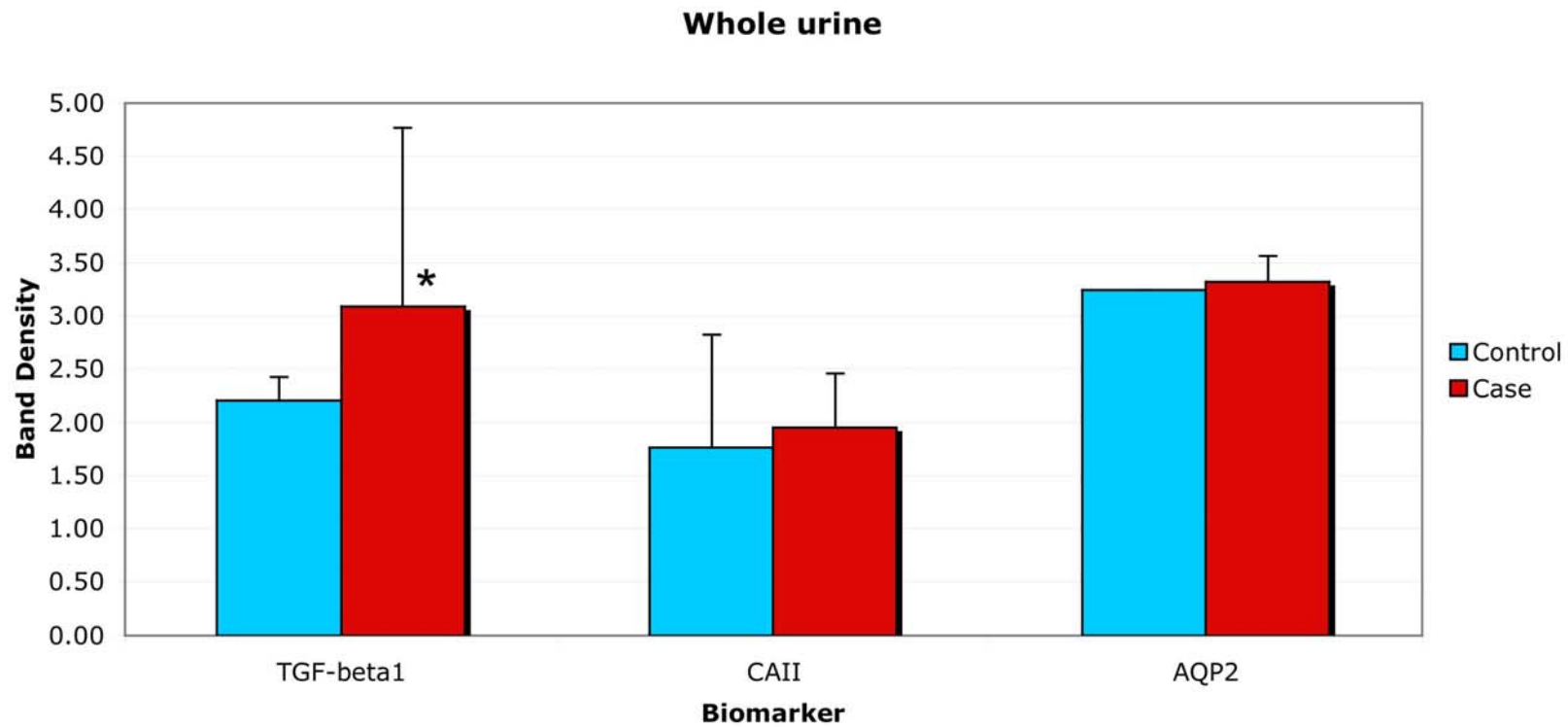


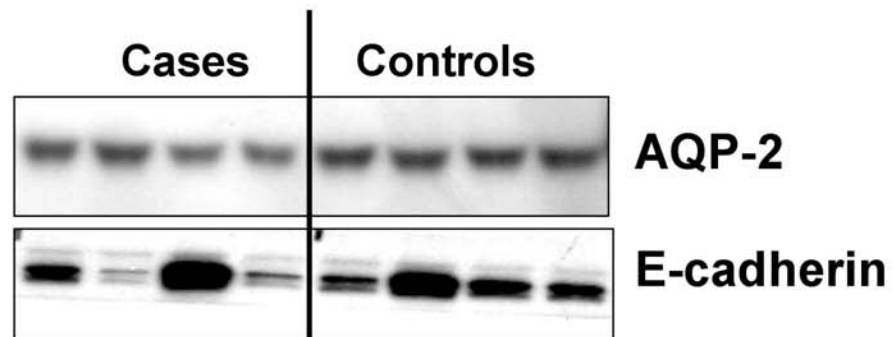
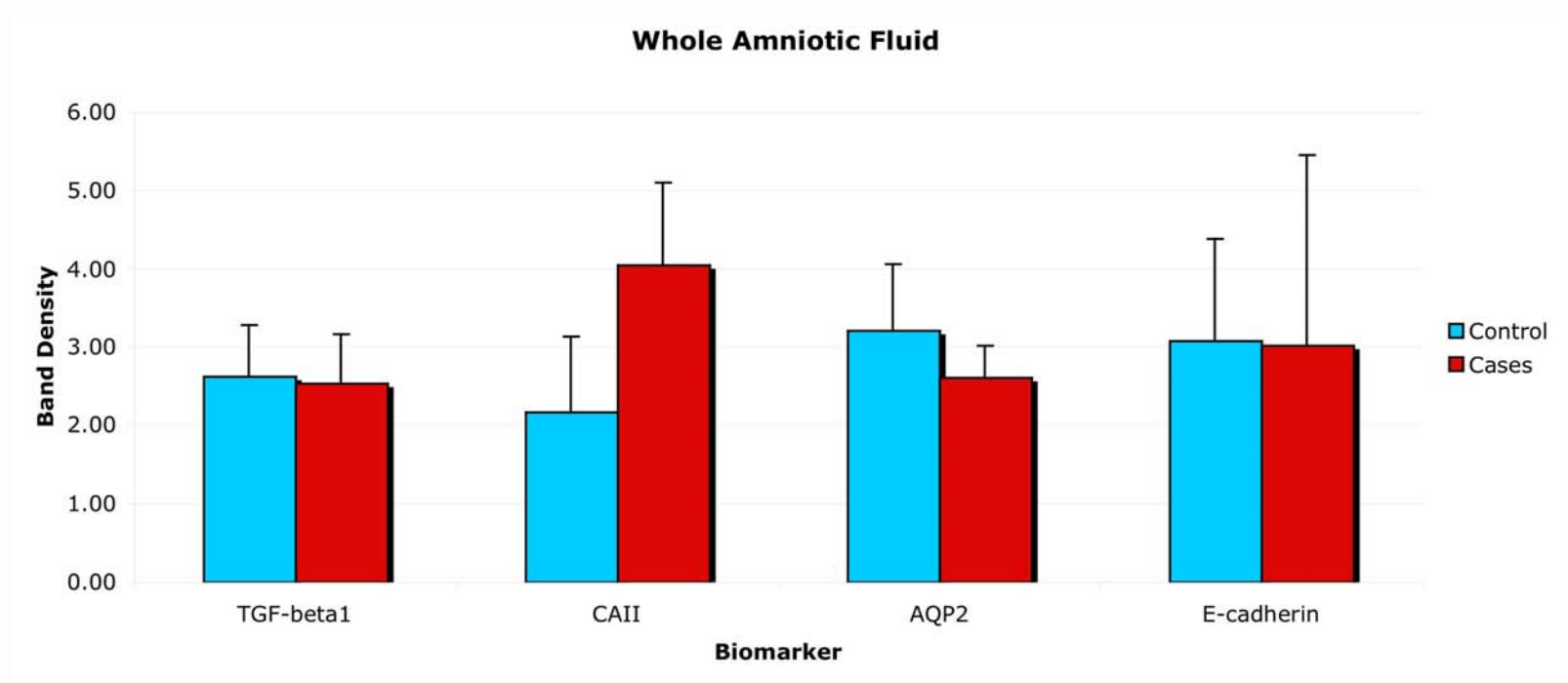
Urine TGF- β 1 Levels



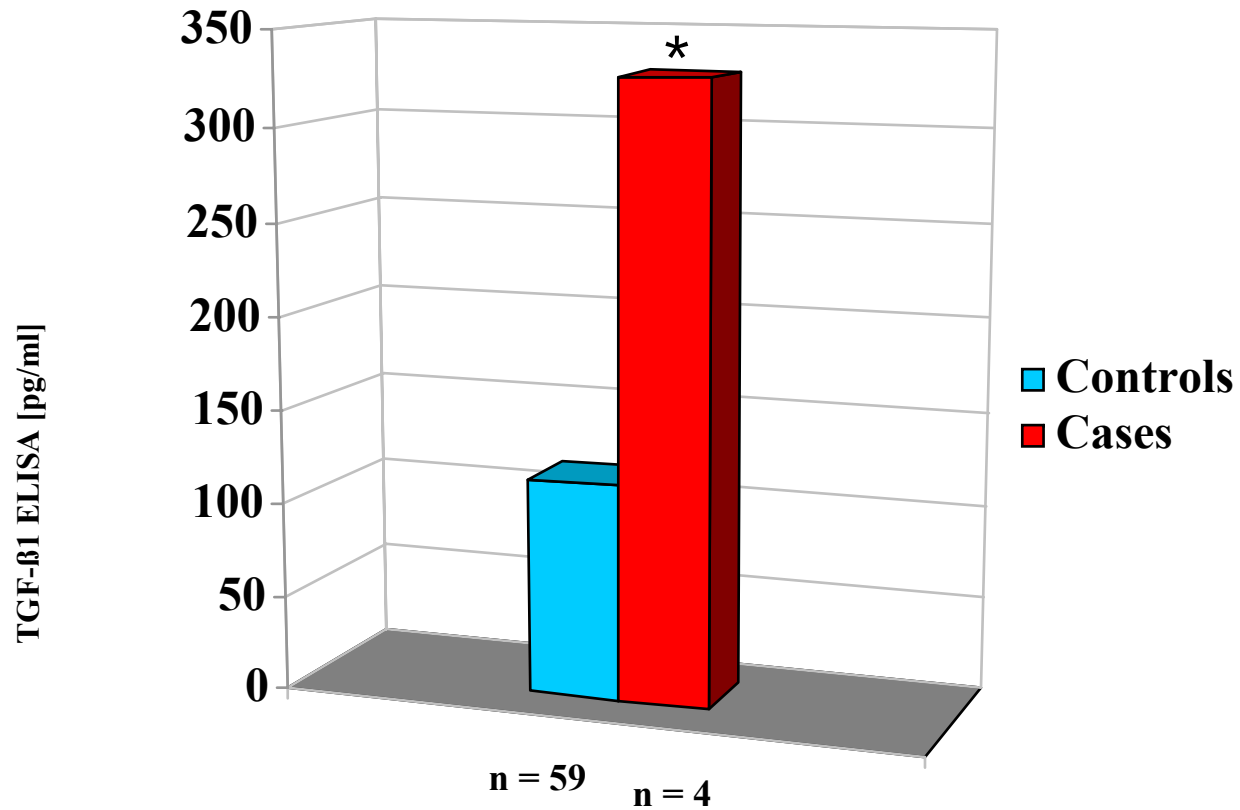
Urine TGF- β 1 in PUV

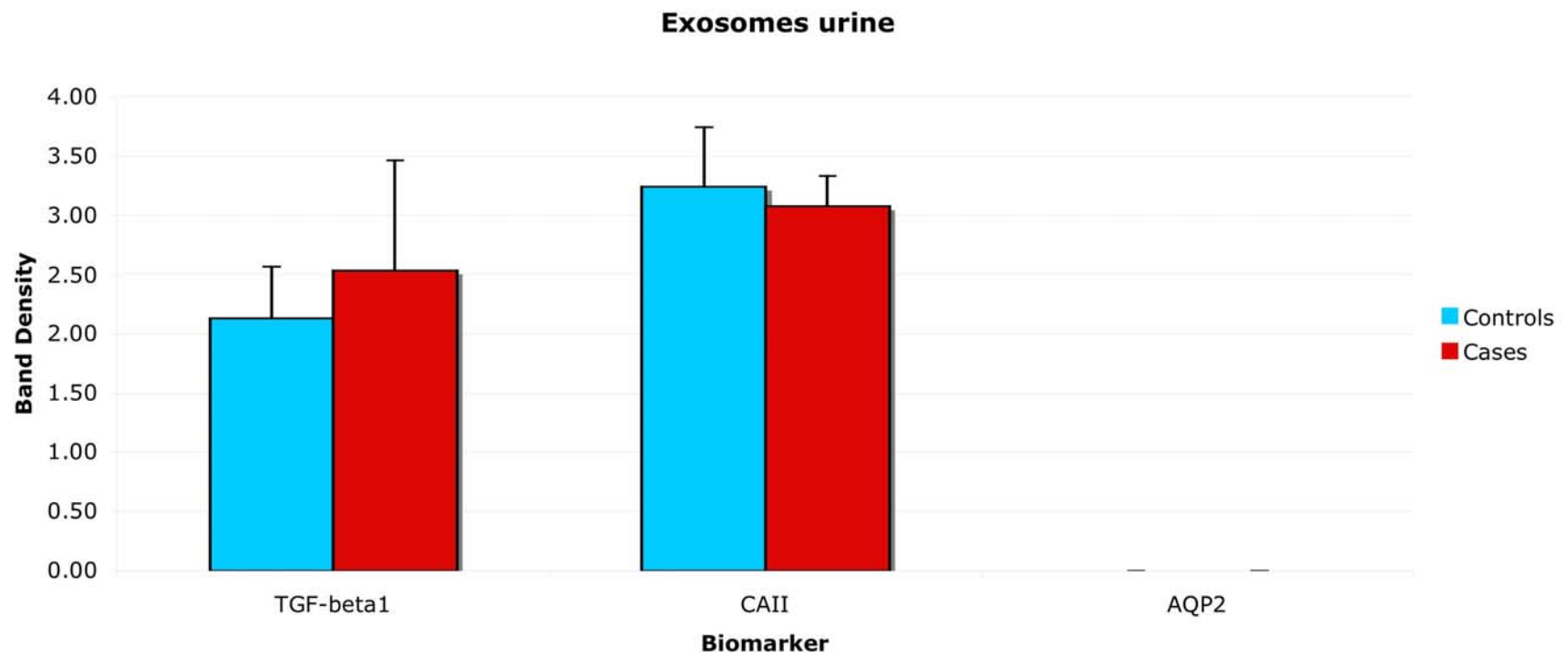




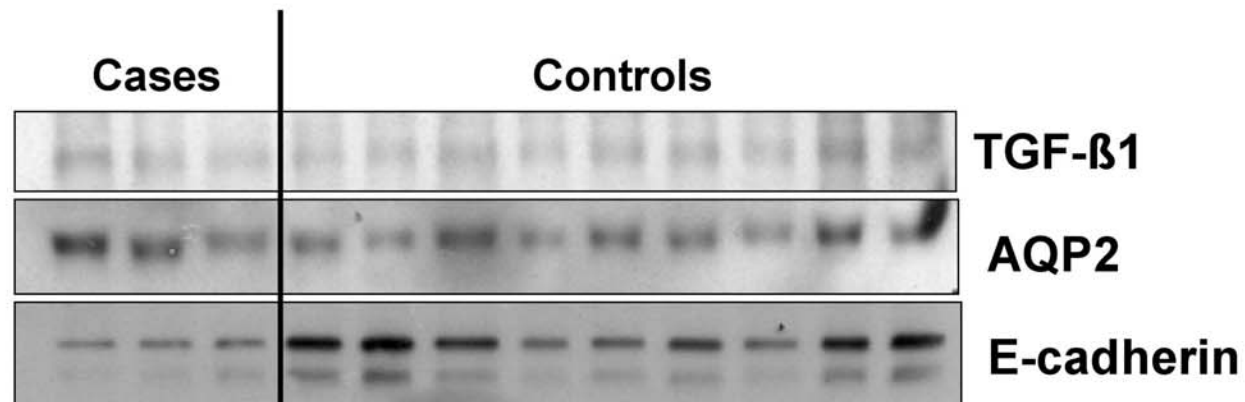
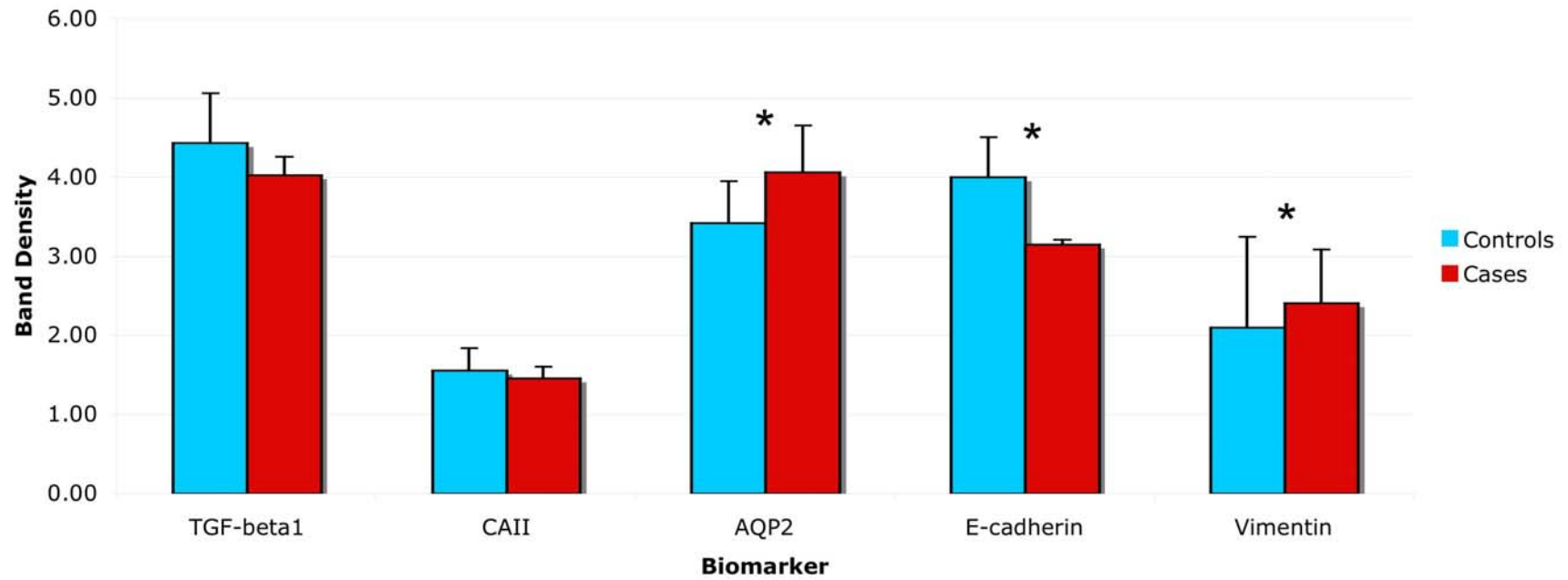


TGF- β 1 in Amniotic Fluid





Exosomes Amniotic Fluid



Summary

- Need for better tests to improve outcome of obstructive fetal renal dysplasia
- Understanding pathophysiology of renal dysplasia helps us to define better biomarkers of this disease
- Our preliminary results show that biomarkers expressed in experimental models can be identified in biological fluids (amniotic fluid, urine) of humans
- Levels of these biomarkers in amniotic fluid, and fetal and postnatal urine may better reflect the severity of renal dysplasia

Anticipated Outcome

- Monitoring levels of biomarkers of fetal renal dysplasia and using the scoring system for severity of renal dysplasia will help in predicting the outcome of these babies and selecting which fetuses should undergo fetal therapy

Thanks to:



&

The families
and the babies
who participate in
the study