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Guido Filler

*Western University*, [guido.filler@lhsc.on.ca](mailto:guido.filler@lhsc.on.ca)

Joanne Grimmer

*Western University*, [joanne.grimmer@lhsc.on.ca](mailto:joanne.grimmer@lhsc.on.ca)

Shih Han Susan Huang

*Western University*

Erika Bariciak

*University of Ottawa*

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## Cystatin C for the assessment of GFR in neonates with congenital renal anomalies

Guido Filler<sup>1,2,3</sup>, Joanne Grimmer<sup>1</sup>, Shih-Han Susan Huang<sup>3</sup> and Erika Bariciak<sup>4</sup>

<sup>1</sup>Department of Paediatrics, Children's Hospital, London Health Science Centre, University of Western Ontario, London, Ontario, Canada, <sup>2</sup>Department of Pathology and Laboratory Medicine, DSB 4044, Schulich School of Medicine and Dentistry, University of Western Ontario, London, Ontario, Canada, <sup>3</sup>Department of Medicine, University of Western Ontario, London, Ontario, Canada and <sup>4</sup>Department of Paediatrics, University of Ottawa, Ottawa, Ontario, Canada

Correspondence and offprint requests to: G. Filler; e-mail: guido.filler@lhsc.on.ca

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### Introduction

It is well-established that the long-term prognosis of renal function in neonates depends largely on their nephron endowment [1]. There is also an increased appreciation that the nephron endowment is not the same for every neonate, and congenital abnormalities, especially those with intermittent or persistent increased pressure in the urinary collecting system, may be associated with a substantial nephron loss. The key mechanism is believed to be the induction of apoptosis-promoting molecules by increased pressure in the urinary collecting system [2]. Initially, it was thought that damage from obstruction to the developing urinary collecting system would be limited to tubular atrophy, interstitial fibrosis and renal tissue loss, whereas glomeruli would not show a significant injury [3], but tubulointerstitial damage affects the glomerular function and promotes the disease progression [4]. The current understanding is that conditions such as high-grade vesicoureteric reflux or obstructive uropathy negatively affect the nephron endowment, which then leads to glomerular hypertrophy, decreased renal function and/or increased proteinuria [5]. Even before birth, all glomeruli are terminally differentiated in humans [1]. A low nephron endowment leads to hyperfiltration with subsequent fewer, larger and more voluminous glomeruli that adapt their filtration surface area while the residual renal reserve is reduced. This has been elegantly shown in patients with primary hypertension [6].

Antenatally, the urinary tract is now assessed in most developed countries by prenatal ultrasound screening in two of three pregnancies [7, 8]. Congenital anomalies of the kidneys and urinary tract are quite common and have an incidence of 0.1–0.7% [7, 8]. The combined incidence rates for children with an anterior–posterior renal pelvis diameter of  $\geq 10$  mm was 0.29%, which is the cutoff considered for the need of postnatal workup by specialists [9]. For nephrologists caring for these children, the

assessment of renal function at birth is important to assess the renal prognosis. Glomerular filtration rate (GFR) remains the most reliable indicator of kidney function and kidney disease progression [10]. The assessment of neonatal renal function remains a challenge, largely because of the impracticability of gold-standard GFR measurements such as inulin clearance, the postnatal adaptation of renal function due to gradual recruitment of nephrons [11] and the fact that the most widely used endogenous marker of GFR, serum creatinine, is affected by maternal renal function for at least 72 h [12]. Creatinine is also insensitive to mildly impaired GFR in all patients [13]. Cystatin C, a novel GFR marker independent of body composition and size [14, 15], is believed to not cross the placenta and thus truly reflects the neonatal renal function [16].

### Cystatin C as a marker of GFR in newborns with congenital anomalies of the kidneys and urinary tract

The characteristics of cystatin C would make it an attractive marker of GFR in newborns with congenital anomalies of the kidneys and urinary tract. In this context, we are delighted to see the manuscript by Parvex *et al.* [17] in this edition of *Nephrology Dialysis Transplantation*. The group studied cystatin C concentrations from cord blood in 33 newborns with an antenatally detected renal pelvis anterior–posterior diameter of  $\geq 10$  mm during the third trimester of pregnancy, as well as 100 term and near-term newborns. The group used an adopted particle-enhanced nephelometric assay (PENIA) derived from an assay (DAKOCytomation) on an IMAGE-BECKMAN analyzer. Their results in the term newborns are considerably higher than reference intervals in the term and preterm infants in whom the Siemens Healthcare cystatin C assay was used [median 2.02 mg/L (3rd percentile 1.54 to 97th percentile 2.64 mg/L) versus 1.84 (3rd percentile 1.32 to 97th percentile 2.63 mg/L)] [12]. Their results were also higher than other previous studies. The reason for this difference is unknown and may be assay-

dependent. Another difference between the current study and previous studies was that Parvex's study used cord blood and not neonatal samples. Renal function matures after birth with the gradual recruitment of nephrons [11] resulting in a rapid decrease in cystatin C levels after birth, but the difference is too large to be explained by this. This points to the need for local assay-specific reference intervals, and its availability clearly was the strength of the study. All children in the current study were born at term; however, it has previously been shown that cystatin C does not change much with prematurity as shown by Bariciak *et al.* [12]. In this previous study, the reference interval in children born between 33 and 36, 28 and 32 and 24 and 28 weeks were 1.89 (0.58–2.93), 1.79 (1.05–2.41) and 1.63 (1.17–2.24) mg/L (no significant difference, Figure 1), respectively. It is unlikely that the observed lower weight in the current study explains the observed differences. Neonatal reference intervals for cystatin C in cord blood have also been reported by another study from Bokenkamp *et al.* [16] and were reported at  $1.66 \pm 0.202$  mg/L (using the DAKO PET-Kit) and a reference interval of 1.26–2.06 mg/L, very close to those reported by Bariciak *et al.* [12].

The main finding was that children with a bilateral kidney malformation had significantly higher cystatin C values than the control group and children with a unilateral kidney malformation. These findings would imply that the renal function and subsequently the nephron endowment are reduced in these patients. This finding is novel and would indeed allow for a simple and non-invasive screening tool independent of maternal serum creatinine.

What was surprising was the fact that neonates with a unilateral kidney malformation had a significantly lower cystatin C than the control group. The decrease in this group was weak, 6.9%. These 20 neonates had a slightly lower weight, which should not have influenced the cystatin C concentrations. This finding would suggest that patients with a unilateral kidney malformation would be hyperfiltering. It is known that the majority of patients with unilateral multicystic kidney disease develop contralateral hypertrophy after a median follow-up of 10 years [18], and perhaps

there is overcompensation already present at birth. However, the finding is unexplained and may be related to the small sample size. Further similar studies should confirm the findings, ideally using appropriate intrarenal volumetry by contrast-enhanced magnetic resonance imaging to determine the nephron endowment by other means [19].

The authors also present a receiver-operated characteristics plot analysis to determine a cutoff for detecting the impaired renal function in the newborn and chose a level of 2.34 mg/L. As shown in Figure 1, this cutoff level may also be applicable for prematurely born newborns with congenital renal anomalies, although it has to be adjusted to the cystatin C assay used.

### Does cystatin C really not cross the placenta?

All the assumptions made in the study by Parvex *et al.* are based on the assumption that cystatin C does not cross the placenta. The study by Parvex *et al.* does not report maternal cystatin C values. Plebani *et al.* [20] and Cataldi *et al.* [21] suggest that cystatin C does not cross the placenta, similar to the findings of Bokenkamp *et al.* [16]. We analyzed the correlation between the maternal and fetal cystatin C in 128 term and preterm newborns in our own data set and found a rather significant correlation between the maternal and newborn cystatin C level ( $P = 0.0297$ , Spearman's rank test, Figure 2, unpublished data). Albeit the correlation coefficient of 0.2243 is low, this would suggest that cystatin C might cross the placenta. The correlation coefficient in Bokenkamp's study was 0.132 [16]. One other previous study also looked at the maternal and fetal cystatin C: Finney *et al.* concluded that the much smaller and statistically insignificant differences between the premature and term cystatin C concentrations suggest a smaller maternal contribution to the neonatal circulatory pool, but suggested some contribution. A longer half-life of cystatin C in the circulation might contribute to the sustained level at Day 7 in term infants [22]. Indeed, cystatin C is thought to be 'more of an HbA1c' of renal function [23].

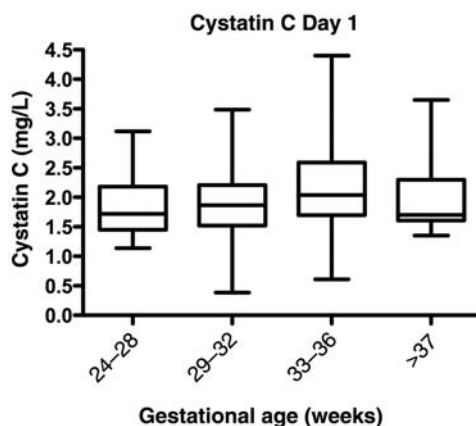


Fig. 1. Box and Whisker plot of cystatin C by gestational age in 128 healthy term and preterm newborns on Day 1 of life.

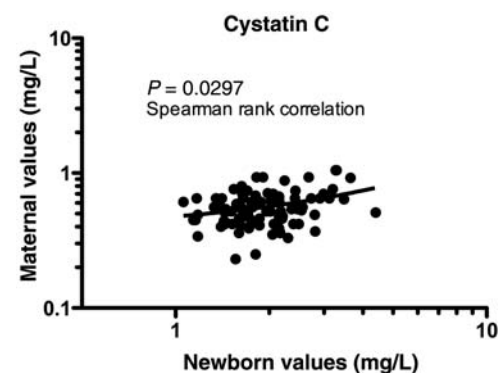


Fig. 2. The relationship between the maternal and newborn cystatin C values in 128 healthy term and preterm newborns (Spearman's  $r = 0.2243$ ,  $P = 0.0297$ ).

It is also noteworthy that cystatin C is not constant in pregnancy. Overall, cystatin C concentrations increase in the third trimester [24]. Most of this appears to be occurring close to term. Cystatin C is also a marker of pre-eclampsia [25]. It is, therefore, possible that some of the findings, especially the lower cystatin C in the patients from Parvex *et al.* [17] with unilateral congenital anomalies, which did have a lower weight, may have had lower maternal cystatin C concentrations, thereby confounding the findings. Future studies on this important topic need to measure maternal values as well as fetal values. These findings will have to be validated with additional small-molecular-weight protein markers of GFR such as  $\beta$ -trace protein, which appears to be a better marker of GFR in pregnancy [24, 26]. It may be important to measure both cystatin C and  $\beta$ -trace protein in these patients.

In conclusion, the study by Parvex *et al.* [17] offers an attractive novel approach to assess the nephron endowment in newborns with congenital renal anomalies. The cutoff value for cystatin C for the identification of neonatal impaired that the nephron endowment should be validated against the local reference intervals. Nonetheless, this study does suggest that low-molecular-weight proteins may indeed serve as promising markers of renal function, at birth, in neonates prenatally diagnosed with congenital kidney anomalies.

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**Conflict of interest statement.** None declared.

(See related article by Parvex *et al.* Is Cystatin C a promising marker of renal function, at birth, in neonates prenatally diagnosed with congenital kidney anomalies? *Nephrol Dial Transplant* 2012; 27: 3477–3482.)

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