MARIANA AFFONSO VASCONCELOS

Modelos de predição em anomalias congênitas dos rins e do trato urinário: Necessidade de cirurgia e progressão para doença renal crônica

Tese a ser apresentada ao Programa de Pós-graduação em Ciências da Saúde área de concentração em Saúde da Criança e do Adolescente da Faculdade de Medicina da Universidade Federal de Minas Gerais como requisito para obtenção do titulo de Doutor.

Orientador: Eduardo Araújo Oliveira

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“Sempre faça tudo com muito amor
e com muita fé em Deus, que um
dia você chega lá. De alguma
maneira, você chega lá”.

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RESUMO

INTRODUÇÃO: As anomalias congênitas dos rins e do trato urinário (Congenital Anomalies of the Kidney and the Urinary Tract - CAKUT) compreendem um grupo heterogêneo de doenças que variam entre alterações dos rins, ureteres, uretra e/ou bexiga. O diagnóstico precoce das uropatias reveste-se de especial importância devido a sua natureza progressiva e seu potencial de irreversibilidade. **OBJETIVOS:** Os objetivos desta tese consistem em uma análise mais abrangente sobre a abordagem cirúrgica de pacientes com CAKUT (estudo1) e uma mais específica que consiste em avaliar a evolução de doença renal crônica (DRC) moderada ou grave em pacientes com válvula de uretra posterior (VUP) (estudo 2). No primeiro estudo, foi desenvolvido um modelo de predição para a necessidade de cirurgia em pacientes com CAKUT e, no segundo estudo, um modelo de predição para evolução para DRC moderada em pacientes com VUP. **ESTUDO 1 - PACIENTES E MÉTODOS:** Estudo de coorte retrospectiva de 694 lactentes com CAKUT admitidos na unidade de nefrologia pediátrica do HC/UFMG de 1987 a 2013. O desfecho primário foi intervenção cirúrgica. A idade mediana de admissão foi de 2 meses e 65% eram do sexo masculino. Considerando as características do paciente à admissão: gênero, idade, creatinina sérica, ritmo de filtração glomerular estimado RFGe, oligohidrâmnio, presença de outras anomalias do trato urinário associadas com dilatação da pelve renal (megaureter, megabexiga), lateralidade da dilatação anteroposterior (DAP) da pelve renal (unilateral ou bilateral), presença de lesões renais na cintilografia estática (DMSA), magnitude da dilatação anteroposterior (DAP) da pelve renal e período de admissão (antes de 2000). Um modelo de predição foi desenvolvido utilizando o modelo de taxas de falhas proporcionais de Cox e a seleção de backward. A validação interna foi obtida através da técnica de bootstrap. **RESULTADOS:** Um total de 164 pacientes (23%) foram submetidos à cirurgia com uma idade média de 7.8 meses. Os preditores inclusos no modelo foram RFGe, presença de outras anormalidades associadas a DAP da pelve renal, presença de lesões renais no DMSA, a magnitude da DAP da pelve renal e o período de admissão. O otimismo do modelo foi de 0.84. **CONCLUSÃO:** O nosso modelo de predição para necessidade de cirurgia em pacientes com CAKUT pode contribuir para identificar pacientes de alto risco para intervenção cirúrgica. Mais estudos serão necessários para validar o modelo em amostras independentes de pacientes com CAKUT. **ESTUDO 2 – PACIENTES E MÉTODOS**: Neste estudo de coorte retrospectiva, 173 pacientes com VUP foram sistematicamente acompanhados na unidade de nefrologia pediátrica do HC/UFMG. Os desfechos primários deste estudo foram

DRC estágio 3 ou maior e DRC terminal. As covariáveis estudadas foram período de admissão (1970-1989 x 1990-2015), apresentação clínica (pré-natal e pós-natal), presença de refluxo vesicoureteral (RVU), lateralidade do RVU (unilateral ou bilateral), creatinina à admissão, RFGe à admissão, nadir de creatinina (menor valor da creatinina durante o primeiro ano após a intervenção cirúrgica), episódios de infecção do trato urinário e intervenção cirúrgica primária. Duas variáveis tempo dependentes foram incluídas na análise: proteinúria e hipertensão arterial sistêmica (HAS). A análise de sobrevida foi realizada através do modelo de taxas de falhas proporcionais de Cox com covariáveis tempo-dependentes. **RESULTADOS:** Depois de um tempo médio de 83 meses, 65 crianças desenvolveram (37.6%) desenvolveram DRC ≥ estágio 3 e 39% (22.5%) atingiram estágio 5. Quatorze pacientes evoluíram para óbito durante o acompanhamento. Trinta e seis pacientes (20.8%) apresentaram HAS e 78 (45%) apresentaram proteinúria durante o acompanhamento. Após o ajuste pelo modelo de Cox variável dependente, creatinina a admissão, nadir de creatinina, hipertensão e proteinúria permaneceram como preditores independentes para DRC maior ou igual ao estágio 3 e DRC terminal. **CONCLUSÃO:** Nossos achados sugerem que a identificação precoce dos fatores de risco passíveis de intervenção clínica podem contribuir para amenizar a progressão da disfunção renal.

PALAVRAS-CHAVE: ANOMALIAS CONGÊNITAS DOS RINS E DO TRATO URINÁRIO, CIRURGIA, HIDRONEFROSE, DOENÇA RENAL CRÔNICA, VÁLVULA DE URETRA POSTERIOR

ABSTRACT

INTRODUTION: Congenital anomalies of the kidneys and the urinary tract (CAKUT) comprise a heterogeneous group of diseases that vary between changes in the kidneys, ureters, urethra and / or bladder. Early diagnosis is important because of its progressive nature and its potential for irreversibility. **OBJECTIVES:** The objectives of this thesis consist of a analysis of the surgical approach of patients with CAKUT (study 1) and a more specific one that consists of evaluating the evolution of moderate or severe chronic renal disease (CKD) in patients with posterior urethral valve (VUP) (study 2). In the first study, a prediction model was developed for the need for surgery in patients with CAKUT and, in the second study, a prediction model for evolution to moderate CKD in patients with VUP. **STUDY1 - PATIENTS AND METHODS:** This is a cohort study of 694 children with CAKUT admitted at the pediatric nephrology unit of our institution. Children were included between 1987 and 2013. The median age at admission was 2 months and 65% were male. Considered patient characteristics at baseline were: gender, age, serum creatinine, estimated glomerular filtration rate (eGFR), oligohydramnios, presence of other urinary tract anomalies associated with renal pelvic dilatation (RPD) (megaureter, megacystis), anteroposterior renal pelvic dilatation (APRPD) laterality (unilateral vs bilateral), presence of renal lesions (RL) on Tc-99m DMSA scan, APRPD magnitude and period of admission (before vs after 2000). A prognostic model was developed using Cox proportional hazard regression analysis and backward selection. Internal validity was studied in 100 bootstrap samples. **RESULTS:** A total of 164 (23%) patients were submitted to surgery at a median age of 7.8 months. The predictors included in the model were eGFR, presence of other urinary tract anomalies associated with RPD, presence of RL on Tc-99m DMSA scan, APRPD magnitude and period of admission. The optimism corrected c statistic was 0.84. **CONCLUSIONS**: Our prognostic model for the need of surgery may contribute to identify CAKUT patients at high risk for surgical intervention. Further studies are necessary to validate the model in independent samples of CAKUT patients. **STUDY 2 - PATIENTS AND METHODS:** In this retrospective cohort study, 173 patients with PUV were systematically followed up at a tertiary Pediatric Nephrology Unit. The primary end-points of the study were CKD stage 3 or higher and ESRD. Survival analyses were performed respectively by Cox regression proportional hazard model with time-dependent covariables. **RESULTS:** After a mean time of 83 months, 65 children (37.6%) developed CKD stage ≥ 3 and 39 (22.5%) reached CKD stage 5. Fourteen (8.1%) died during follow-up. Thirty-six patients (20.8%) presented

hypertension and 78 (45%) exhibited proteinuria during follow-up. After adjustment by the time-dependent Cox model, baseline creatinine, nadir creatinine, hypertension, and proteinuria remained as independent predictors of CKD ≥ stage 3 and ESRD. **CONCLUSION:** Our findings suggest that an earlier identification of risk factors amenable to clinical intervention might contribute to slow the progression of renal impairment.

KEY WORDS: CONGENITAL ANOMALIES OF KIDNEY AND URINARY TRACT, SURGERY, HYDRONEPHROSIS, CHRONIC KIDNEY DISEASE, POSTERIOR URETHRAL VALVE

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LISTA DE ABREVIATURAS E SIGLAS

ANH	Antenatal hydronephrosis
APD	Anteroposterior diameter
APRPD	Anteroposterior renal pelvis dilatation
AUC	Area under the curve
CAKUT	Congenital anomalies of kidney and urinary tract
CI	Confidence interval
CIC	Clean intermitent catheterization
CKD	Chronic kidney disease
CNVs	Copy number variations
DAP	Diâmetro anteroposterior
DRS	Diuretic renal scintigraphy
DMSA	99m-Tc ácido dimercaptosuccínico / 99m- Tc dimercaptosuccinic acid
DRC	Doença renal crônica
DRF	Differencial renal function
DTPA	99m-Tc ácido dietilenotriaminopentacético / 99m- Tc dimercaptosuccinic acid
eGFR	Estimated glomerular filtration rate
ESRD	End stage renal disease
HAS	Hipertensão arterial sistêmica
HR	Harzard ratio
IC	Intervalo de confiança
IRR	Inter-rater reliability
ITU	Infecção do trato urinário
KID	Kids` Inpatient Database
LUTO	Lower urinary tract obstruction
MAG3	99m-Tc ácido mercaptoacetiltriglicinico /99m- Tc mercaptoacetyltriglycine acid
MCDK	Multicystic dysplastic kidney
OJUP	Obstrução da junção uretero-pélvica
OR	Odds ratio
PLUTO	Percutaneous shunting in lower urinary tract obstruction
POM	Primary obstructive megaureter
PT	Parenchymal thickness
PUV	Posterior urethral valve

RBUS Renal and bladder ultrasonography

RUS Renal and urinary ultrasonography

RL Renal lesions

RDM Rim displásico multicístico

ROC Risk operating curve

RPD Renal pelvis dilatation

RR Relative risk

RVU Refluxo vesicoureteral

SFU Society of fetal urology

UCM Uretrocistografia miccional

UE Urografia excretora

UPJO Ureteropelvic obstruction

US Ultrasonography / ultrassonografia

UTD Urinary tract dilatation

UTI Urinary tract infection

VAS Vesico-amniotic shunting

VCUG Voiding cystourethrogram

VUP Válvula de uretra posterior

VUR Vesicoureteral reflux

VURD Posterior uretral valve, unilateral vesicoureteral reflux and renal dysplasia

SUMÁRIO

1. INTRODUÇÃO

As anomalias congênitas dos rins e do trato urinário (Congenital Anomalies of the Kidney and the Urinary Tract - CAKUT) compreendem um grupo heterogêneo de doenças que variam entre alterações dos rins, ureteres, uretra e/ou bexiga. Junto com as anomalias congênitas do sistema nervoso central, compreendem as principais malformações ao nascimento. Sua prevalência varia 1-5% das gestações (1, 2). Dentre as causas mais comuns estão o rim displásico multicístico, estenose de junção uretero-pélvica, refluxo vesicoureteral (RVU) e válvula de uretra posterior (VUP) (3).

O diagnóstico precoce das uropatias reveste-se de especial importância devido a sua natureza progressiva e seu potencial de irreversibilidade. Estas anomalias são, quase sempre, assintomáticas ao nascimento e, mesmo com uma palpação abdominal cuidadosa visando à procura minuciosa de malformações do trato urinário, a incidência encontrada é muito inferior da incidência estimada por estudos de necropsia (4). O diagnóstico é, então, frequentemente, obtido após a criança apresentar complicações tais como infecção do trato urinário (ITU), hipertensão arterial sistêmica (HAS), atraso no crescimento e, algumas vezes, uma lenta e silenciosa deterioração da função renal. Por conseguinte, as CAKUT são responsáveis por 20 a 35% das causas que levam à doença renal crônica (DRC) em crianças (5).

Nos últimos anos, houve crescente avanço na compreensão da fisiopatologia, das bases genéticas e da história natural das CAKUT (3, 6-15). Entretanto, há ainda várias controvérsias a respeito do significado clínico da detecção pré-natal dessas condições. Um dos principais dilemas em relação às CAKUT é identificar as anomalias que predispõem ao desenvolvimento de complicações como HAS, ITU e DRC e quais irão se beneficiar da intervenção cirúrgica (16). A seguir serão discutidos alguns pontos ainda polêmicos como a indicação cirúrgica em CAKUT e a evolução para DRC em pacientes com VUP.

Muita dúvida ainda existe a respeito de qual é melhor tratamento de pacientes com CAKUT: conduta expectante ou intervenção cirúrgica precoce (1, 9, 17-25). Ainda, não existe um exame padrão ouro que determine qual paciente irá necessitar de um manejo mais agressivo. Os principais exames de imagem realizados em pacientes com CAKUT são: a ultrassonografia de rins e vias urinárias, uretrocistografia miccional (UCM), cintilografia renal estática e dinâmica (17, 26).

Sobre os achados ultrassonográficos, comparados à população normal, pacientes com hidronefrose fetal têm maior risco de uma doença pós-natal (1). A maioria dos casos de hidronefrose leve evolui com resolução espontânea (19, 20, 27). Já a incidência de uropatia aumenta proporcionalmente da dilatação leve a grave (1, 28).

A UCM é um exame utilizado na investigação de doenças do trato urinário baixo e como triagem de RVU, no entanto, trata-se de um exame mais invasivo que causa muita ansiedade nos pais e crianças (29).

Quanto ao exame de cintilografia renal, os mais usados são 99Tc-ácido dietilenotriaminopentacético (DTPA), 99Tc-ácido dimercaptosuccínico (DMSA) e 99Tc-ácido mercaptoacetiltriglicinico (MAG3). As indicações clássicas de cirurgia são a detecção de curva de eliminação com padrão obstrutivo, função renal relativa menor do que 40% ou perda da função renal relativa maior do que 10% em exames consecutivos (29-31). Infelizmente, esses exames apresentam limitações e isoladamente não são bons preditores de obstrução (29).

O tipo de manejo é determinado de acordo com achados laboratoriais, de imagem e clínicos. No entanto, os melhores parâmetros ainda não estão bem estabelecidos (1, 6, 26, 29, 32). Alguns autores justificam uma intervenção precoce para evitar que os pacientes evoluam com perda progressiva do parênquima e infeções do trato urinário; no entanto, outros justificam o manejo conservador já que muitas alterações do parênquima são congênitas e irreversíveis (18, 29, 33-39).

Outro tópico ainda pouco estudado na literatura em CAKUT diz respeito à VUP. VUP é a anomalia obstrutiva congênita mais comum da uretra com uma incidência de 1 para 3000 a 8000 nascimentos (40). Ela está relacionada à obstrução congênita do trato urinário num momento crítico da organogênese, que pode causar profundo impacto na formação dos rins, ureteres e bexiga (41, 42).

A morbidade associada à VUP estende-se da infância à vida adulta. Sua taxa de mortalidade diminuiu significativamente nas últimas décadas de 50% para menos do que 5% (43, 44). No entanto, com o avanço no diagnóstico e manejo, mais pacientes têm enfrentado sequelas em longo prazo, que incluem DRC, disfunção miccional e disfunção sexual e reprodutiva (45-47).

A VUP é uma causa comum de DRC, mas pouco se sabe quais pacientes irão progredir rapidamente para DRC e quais irão ter uma progressão mais gradual (48-51).

As taxas de progressão para DRC variam na literatura de 22 a 68% (44, 52). Alguns fatores preditivos têm sido associados com a ocorrência de DRC terminal, incluindo oligoidrâmnio, creatinina plasmática inicial elevada, nadir (menor valor) da creatinina plasmática dentro de um ano após descompressão, necessidade de suporte ventilatório, presença de RVU bilateral, diagnóstico tardio, disfunção da bexiga, atraso na aquisição da continência urinária e infecções do trato urinário (49, 52-54).

Nas últimas décadas, a Unidade de Nefrologia Pediátrica do Hospital das Clínicas da UFMG tem estudado pacientes portadores de uropatias com diagnóstico pré e pós-natal e desenvolvido diversas pesquisas clínicas na tentativa de uma melhor compreensão desse grupo heterogêneo de doenças. Pretende-se, em última instância, estabelecer diagnóstico mais precoce e preciso e seguimento clínico adequado à condição de cada paciente, ou seja, condutas mais intervencionistas em pacientes de alto risco para evolução desfavorável (DRC, HAS, ITU) e condutas mais conservadoras nos casos de baixo risco.

Portanto, o presente estudo se insere em uma linha de pesquisa mais ampla compreendendo diversos aspectos clínicos, laboratoriais e marcadores das anomalias congênitas do trato urinário. Mais recentemente, têm sido desenvolvidos no serviço modelos de predição de desfechos clínicos em CAKUT, visando identificar pontos ainda controversos na conduta de pacientes de CAKUT, mais especificamente, a indicação de intervenção cirúrgica e a evolução para DRC nos pacientes com VUP (55).

Assim, a tese de doutorado será constituída no seu formato final em dois artigos de revisão: (1) Abordagem cirúrgica x conservadora do CAKUT (2) Válvula de uretra posterior: desfechos clínicos e manejo; e dois artigos originais (1) Modelo de predição clínica da necessidade cirúrgica em casos de CAKUT (2) Modelo de predição clínica de desfechos para DRC em casos de válvula de uretra posterior. As referências bibliográficas estão dispostas ao final de cada artigo ou seção. Para as citações do texto foi utilizado o sistema denominado Vancouver, elaborado por um grupo de editores das principais publicações biomédicas internacionais na cidade de Vancouver, no Canadá, em 1979 e atualizado em 2004 (Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication - www.ICMJE.org).

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2. ARTIGOS DE REVISÃO

2.1. Artigo de revisão I

Congenital Anomalies of Kidney and Urinary Tract: The issue of surgical versus non-surgical management

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Abstract

Congenital anomalies of kidney and urinary tract (CAKUT) comprise a heterogeneous group of pathologies that affect kidney and urinary tract. They are main responsible for urinary tract infection (UTI), chronic kidney disease (CKD) and end stage renal disease (ESRD) in children. However, there are still controversies about the best parameters and timing to submit patients to surgical procedure. It is important to avoid unnecessary intervention, but a late procedure could submit patients to infection and renal parenchymal loss. Despite the evolution in imaging exams and biomarkers, there has not been so far a gold standard exam to define surgical treatment. Nevertheless, the natural history of CAKUT has shown that the best management in most cases is non-surgical. Currently, non-surgical management of CAKUT should be considered whenever possible for infants with ANH.

Keywords: Congenital anomalies of urinary tract; Antenatal hydronephrosis; Hydronephrosis; surgery; ureteric pelvic junction obstruction; vesicoureteral reflux obstruction; primary obstructive megaureter; multicystic dysplastic kidney; posterior urethral valves

Introduction

Congenital anomalies of kidney and urinary tract (CAKUT) are a heterogeneous group of diseases that affect kidney and urinary tract. They comprise anomalies in the kidneys, ureters, bladder and urethra like ureteric pelvic junction obstruction (UPJO), vesicoureteral reflux (VUR), multicystic dysplastic kidney (MCDK), primary megaureter, obstructing megaureter, ureterocele, ectopic kidney and posterior urethral valve (PUV) (1-6). CAKUT are one the most common congenital anomalies and occurs in 1 in 500 to 16 in 1000 live births with predominance of male gender (1-3, 5, 7-11). Of note, Mallik et al have detected an increase in the incidence of CAKUT during recent years (1).

Antenatal hydronephrosis (ANH) is a surrogate marker of potential congenital renal anomalies. Nevertheless, ANH usually cannot identify any specific uropathy. Currently, the measurement of the anteroposterior renal pelvic diameter (APRPD) is the most studied parameter for assessing ANH. Nevertheless, it is clear that establishing a simple threshold APRPD value that separates normal from abnormal situations is a challenging task. The definition of ANH varies according to studies protocols between 4-7 mm of APRDP in the 3rd trimester (2, 12). There is no consensus of the optimal APRDP threshold for determining postnatal follow up (12). Some studies classify ANH into three categories according APRDP in the third trimester: mild < 9 mm, moderate 10-15 mm and severe ≥ 15 mm (2, 13). The most common presentation is a mild dilation (3). In 1993, the Society for Fetal Urology (SFU) proposed a 4 point numerical grading system based on the postnatal appearance of the renal pelvis, calyces, and renal parenchyma (14). According to this system, no splitting corresponds to SFU grade 0, urine in pelvis barely splits sinus corresponds to SFU grade 1, full pelvis and major calyces dilated corresponds to SFU grade 2, uniformly dilated minor calyces and parenchyma spared corresponds to SFU grade 3 and SFU grade 4 corresponds to SFU3 plus reduction of renal parenchyma (12, 14).

The importance of precocious diagnosis and management of CAKUT lies in the fact that they are the principal responsible for urinary tract infection (UTI), chronic kidney disease (CKD) and end stage renal disease (ESRD) in children (9, 15-18). The majority of CAKUT is non-surgically managed, but, in some cases, surgery will be obviously necessary (2, 6, 10, 19-21). Gokce et al. found a rate of surgery of 30% in patients with antenatal urinary tract anomalies (9). However, Mallik et al found an

incidence of 7% in their cohort study (1). Nef et al. prospectively studied 115 children with prenatally diagnosed with CAKUT and found that oligohydramnios and postnatal bilateral anomalies were significantly associated with surgery and impaired renal function (6). Nevertheless, there are still controversies about the best parameters and timing to submit patients to surgical procedure (1, 2, 12, 22, 23). It is important to avoid unnecessary intervention, but a late procedure could submit patients to infection and renal parenchymal loss (12). So far, there has not been yet identified a gold standard test to define which patient will need surgery. In this context, the aim of this review is to compile literature evidence about the issue of surgical versus non-surgical management of CAKUT.

Objective: Compile the literature evidence about the issue of surgical versus non-surgical management of CAKUT.

Methodology: A review articles was conducted using PubMed. Included studies reported at least one of the following items: congenital anomalies of kidney and urinary tract, antenatal hydronephrosis, vesicoureteral reflux, ureteric pelvic junction obstruction, multicystic dysplastic kidney, megaureter, ureterocele, posterior urethral valve, antenatal diagnosis, postnatal management.

Postnatal imaging evaluation

The postnatal evaluation of ANH has been a topic of debate and controversy. The understanding that any degree of ANH can be associated with significant uropathy can set the stage for deriving a consistent approach to the evaluation of these infants. The difficulty in establishing a standardized approach is related to the complexity and variability of the kidney and urinary tract anomalies. On one hand, CAKUT comprises an intricate spectrum of malformations that can occur at the level of the kidney, ureters, bladder, or urethra (24). On the other hand, more than half the cases of ANH resolve by the end of gestation or during the first year of life (25). For instance, Madden-Fuentes et al (26) followed-up 416 infants with SFU grade I or II and showed that low-grade urinary tract dilation (UTD) diagnosed within the first year of life remains stable or improves in 97.4% of renal units.

Renal imaging has a central role in the investigation and follow-up of these infants. The information concerning the features of prenatal ultrasonography is essential to guide postnatal evaluation and management. Upper UTD is the most common renal

anomaly detected prenatally, and both vesicoureteral reflux (VUR) and ureteropelvic junction obstruction (UPJO) should be considered. Renal parenchyma disease can be recognized in the fetus by cystic changes or by the appearance of abnormal echogenicity of the renal parenchyma. The fetal bladder is a critical structure in the evaluation of the lower urinary tract (27).

There are several imaging modalities commonly used in the postnatal evaluation of ANH, including renal ultrasound (US), voiding cystourethrography (VCUG), and diuretic renal scintigraphy (DRS). The ultimate goal of any imaging strategy is to detect which patients would benefit from surgical intervention and which may be best assisted by continued surveillance (28). Nevertheless, many aspects concerning postnatal imaging evaluation of ANH are still controversial. In this regard, in 2010, the SFU published the consensus statement on the evaluation and management of ANH(12). The consensus stated that, as evidenced by the current literature, the optimal schedule for postnatal evaluation of children with ANH is unclear. The consensus suggests an individualized approach, based on certain characteristics including the degree of UTD, laterality, suspected ureter, bladder and urethral abnormalities, and amniotic fluid status (12).

The guiding principle in imaging must be to undertake appropriate investigations using the lowest radiation and least invasive techniques possible (29). For this purpose, renal US is the first imaging exam to be performed after birth. Renal US findings determine the extent and the need for further investigations (2). As mentioned, most of minimal hydronephrosis will resolve spontaneously during the first year of life (11, 30, 31). The incidence of urological diseases increases significantly from mild to severe dilation (2, 3). According to Lee et al., the risk of uropathy is 11.9% for mild, 45.1% for moderate and 88.3% for severe ANH (2). De Kort et al. showed that children with mild to moderate ANH have low risk of UTI (3.8%) and surgical interventions (0.9%) as compared with moderate to severe ANH (26.3% and 36.8%, respectively) (32). In addition, Barbosa et al. described that most mild and moderate cases are not associated with uropathies and more than a half of severe cases require surgery (32, 33). In contrast, Chertin et al. showed that 50% of children with moderate ANH require surgery (34). Blachar et al. found that fetal APRDP higher than 9 mm is predictive of surgery (35), while Plevani et al. reported the association between a mean antenatal APRDP superior to 15 mm with uropathy and surgery and proposed a cutoff of 7 mm at the third

trimester to predict neonatal nephrouropathy (11). In a systematic review of the literature, Passerotti et al. detected that 8% of patients with normal renal pelvic diameter or mild hydronephrosis at the first postnatal US had UPJO or ureteral obstruction (3). This finding shows that infants should be followed up until the certainty on the absence of any uropathy. Renal parenchyma thinning is another US feature frequently correlated with uropathies (3). Several studies have shown that neonatal renal US has good accuracy in identifying clinically significant AHN (36, 37). In a retrospective study, Rianthavorn and Limwattana (38) showed that an APRPD > 16 mm and SFU grade IV are good cut-off points in identifying significant hydronephrosis with areas under the receiver operating characteristic (ROC) curve of 0.86 and 0.81, respectively. Of note, Vemulakonda et al. have assessed the inter-rater reliability (IRR) of the SFU grading and of the APRPD and have concluded that the SFU grading is associated with excellent IRR, although the APRDP seems to have higher IRR(39).

Table 1 resumes studies of ANH and risk of renal pathology.

Table 1

Another imaging test to be considered in the investigation of AHN is the voiding cystourethrogram (VCUG). VCUG is absolutely indicated as an immediate postnatal study for neonates with suspected bladder outlet obstruction, most commonly posterior urethral valve (PUV) (40). In addition, VCUG may be helpful in the evaluation for VUR, megaureters, ureteroceles, and renal duplication anomalies. However, this is an invasive method with radiation exposure and possible adverse effects (12). Although the recommended use of VCUG for severe hydronephrosis (SFU grades 3 to 4) has been well-established, the need for VCUG in the workup of patients with mild to moderate hydronephrosis (SFU 2 or less) remains controversial (28). VUR accounts for about 10 to 15% of urinary tract anomalies associated with ANH. Most studies have shown that a single postnatal US is unable to predict the presence or severity of VUR. However, as the definition of clinically significant VUR continues to evolve, so does the role of screening VCUG (39).

The SFU consensus recommends VCUG for infants with persistent moderate-severe UTD, bilateral UTD, and/or the presence of ureteral, bladder, and urethral abnormalities on postnatal US. However, some centers advocate detailed investigations and others indicate a less invasive approach (41). Two new studies highlighted the

diversity regarding this issue. Vemulakonda et al. (39) performed a retrospective study to identify geographic variability in the imaging of infants with AHN. The authors showed that the use of VCUG is highly variable across sites (17.6%-88.9%) even after controlling for age and hydronephrosis grade. Interestingly, the use of other imaging studies did not differ significantly across sites. Braga et al. (42) performed a survey to ascertain practice patterns for obtaining VCUG in infants with AHN by pediatric nephrologists and urologists across Canada. Regarding the indications for VCUG, 31% of pediatric nephrologists would recommend this test for patients with unilateral low-grade AHN compared with 7.7% of urologists, although almost all nephrologists (96.6%) and 69.2% of urologists would obtain this test for patients with unilateral high-grade isolated AHN. Some studies have proposed criteria for the safe omission of VCUG in postnatal management (43, 44). For instance, Lee et al. (43) have suggested that VCUG should be recommended only if the US has one of the following findings: presence of hydroureter, renal dysmorphia or duplication. By using these criteria, they found that low- and high-grade VUR would have been missed in 33% and 17% of the cases, respectively, although this appeared to be of low clinical significance.

DRS is the most commonly imaging modality used to determine the presence of upper urinary tract obstruction in infants with ANH. The SFU currently recommends DRS for the following patients without VUR: moderate unilateral ANH with persistent postnatal hydronephrosis, severe ANH regardless of postnatal US findings, moderate or severe postnatal hydronephrosis, any hydronephrosis with bladder or urethral abnormalities, any hydronephrosis with dilated ureter, and any hydronephrosis associated with decreased amniotic fluid. The most common type of nuclear renography used in cases of suspected obstruction utilizes the Tc-mercaptoacetyltriglycine (MAG3) radiotracer, permitting the measurement of both differential renal function (DRF) and renal drainage. An initial renogram is generally obtained at least 6 to 8 weeks after birth to allow renal maturation. The diagnostic accuracy of DRS has been reported to be highly variable. In a notable review, Ismaili & Piepsz (45) outlined the advances, pitfalls and difficulties in the interpretation of renography for the evaluation of upper tract obstruction in infants. Interestingly, in a well-designed study, the same group concluded that DRS should only be performed in patients with APRPD >30 mm, major calyceal dilatation and/or renal parenchyma thinning.

The typical surgical recommendations for ANH are obstructive wash-out curve and relative renal function less than 40% or reduction superior to 10% of renal function in sequential renograms (12, 46, 47). Unfortunately, these exams have limitations in the prediction of ureteral obstruction (12).

New biomarkers are promising tools for the improvement of the diagnosis and management of CAKUT (48-50). Measurements of inflammatory and fibrogenic molecules in urine samples and proteomic analysis have shown relevant results (48-50). However, these methods are not available in clinical practice. Ultimately, the aim of submit the patient to urologic surgery is avoid the progression of kidney lesions and new urinary tract infections episodes, consequently, delaying the progression of CKD.

Management of specific uropathies

Ureteric pelvic junction obstruction (UPJO)

UPJO is the most common obstructive uropathy in children with an incidence of about 4.2 per 1000 births (5, 7, 9, 10). The primary structural anomaly may be attributed to a malfunction in smooth muscle cells of the ureter (51). Males are most commonly affected and this anomaly is usually unilateral with predominance of the left side (3, 19, 34). The management of UPJO is still a matter of debate. Traditionally, the treatment of choice for UPJO was surgical. However, owing to the prenatal diagnosis and consequent better understanding of the natural history of UTD, the potential for spontaneous resolution of UPJO over time has been demonstrated (28). However, the ability to define which children will resolve their condition or will benefit from a surgical procedure remains elusive (52). Arora et al. (53) reported a prospective single center study involving 122 renal units with ANH. A multivariate analysis revealed APRPD and preoperative DRF on DRS as the only independent predictors for the need of surgery. ROC curve analysis showed that an APRDP of 24.3 mm could predict the need for surgery, with a sensitivity of 73.1% and a specificity of 88.0%. Most observational protocols recommend surgery if patients show a DRS with obstructive washout curve, DRF < 40%, decreased DRF > 10% on serial DRS, and progression of hydronephrosis on serial US (54). For non-surgically managed patients, the time and frequency of follow-up imaging must be individualized based on clinical experience and judgment (28, 45, 52). The management of UPJO varies from non-surgical approach with long-term clinical follow-up to surgical intervention, including pyeloplasty,

nephrostomy and nephrectomy (19, 34, 55, 56). Approximately, 19-25% of UPJO patients require surgery (11, 12, 57, 58). On the other hand, Chertin et al. found a prevalence of 50% of surgery in patients with initial non-surgical management (34).

The parameters used to indicate surgical intervention are the magnitude of APRDP, the progression of APRDP, renal cortex thickness, diuretic renography curve, DRF and presence of complications like UTI and pain (11, 34, 47, 54). The degree of hydronephrosis has strong correlation with the diagnosis of UPJO, but not all patients will need surgery (3). Longpre et al. studied 100 patients with ANH and found that high values for initial APRDP (mean initial APRDP 29 mm) predict the need for surgery (59). Mudrik-Zohar et al. analyzed infants with isolated hydronephrosis and found APRDP and parenchymal thickness (PT) as predictors for postnatal pyeloplasty. ROC curve analysis showed that a 14mm cutoff for APD (area under the curve of 0.817) had a sensitivity of 77% and specificity of 69% and an APRDP/PT ratio of more than 2.1 had sensitivity of 87% and specificity of 65% for predicting the need of surgery (area under the curve of 0.822) (54). In a cohort study of newborns with isolated ANH, Dias et al. found that a cutoff of 18 mm for fetal APRPD and a cutoff of 16 mm for postnatal APRPD have the best diagnostic odds ratio to identify infants who needed pyeloplasty (37).

The diagnostic value of renography is mainly to exclude obstruction than to confirm (47). DRF less than 40% is an indicative of surgery, but Huang et al. showed that normal radionucleotide uptake did not necessarily reflect normal renal parenchyma (60). Only severe alterations in renal parenchyma are associated with significant reduction of renal function on renography (60). Otherwise, Han et al. speculated that reduction in differential renal function correlates with histological damage (61). Chertin et al. detected RRF <40% and moderate to severe postnatal hydronephrosis as independent predictors for surgery (34).

The indication of surgical intervention for pediatric patients has decreased, while there has been an increasing trend toward non-surgical management (56, 62). Most of renal parenchymal alterations have already occurred during the antenatal period, which possibly justify the usefulness of surgical intervention in many cases (60, 61, 63, 64). For instance, in some patients with unilateral UPJO, there is no difference in DRF after surgery because kidney damage had probably occurred at the antenatal period (47, 64, 65). Gordon et al. did not found a substantial change of function in patients submitted to

surgery in comparison to non-operated group (47). Calisti et al. retrospectively studied 84 patients and the renal function of prenatally detected cases was not influenced by early or delayed surgery (64). Insignificant functional loss has been recorded among some cases operated after non-surgical management (64). Notwithstanding, some authors advocate early intervention because of progressive alterations of renal parenchyma (34, 60, 66-71). For instance, Huang et al. studied kidney biopsies of 61 patients with UPJO and found tubular changes associated with interstitial fibrosis more frequently in patients who underwent surgery with more than 1 year of age (60). This finding suggests that congenital hydronephrosis may be a deleterious and progressive condition (60) Sheu et al. evaluated retrospectively 102 patients with UPJO and detected an improvement more than 5% in 61.5% of patients submitted to pyeloplasty (66). In addition, Subramaniam et al. analyzed 121 children with UPJO and found lower improvement of renal function in patients submitted to delayed pyeloplasty compared to early pyeloplasty (67). In the same way, Yang et al. reported that patients with SFU grades 3 and 4 hydronephrosis need early surgical procedure for preserving renal function (69).

Table 2 resumes predictors of surgery and UPJO.

Table 2

Vesicoureteral reflux (VUR)

VUR is also a common urinary tract anomaly with an incidence of 3.6 per 1000 births with male predominance among those cases detected after investigation of ANH (7, 9). However, Skoog et al. found the same prevalence in male and in females among siblings (72). Children with ANH have an increased risk of VUR compared to general population (2). During investigation of patients with ANH, VUR incidence was 12-16% of patients (1, 72). It is the most common cause of hypo/dysplastic kidney (73). The accuracy of both antenatal and postnatal ultrasounds is poor to detect VUR (7, 74). The severity of hydronephrosis is not associated with presence or grade of VUR (2, 3, 33, 72, 75). Lee et al. did not find an association between the grade of ANH and the risk of VUR (2). Accordingly, Dias et al. reported that fetal and postnatal renal pelvic dilatation were poor predictors of VUR (41). On the other hand, they found that fetal and postnatal renal pelvic diameter less than 10 mm make the diagnosis of VUR improbable

(41). In addition, de Kort et al. showed an association between antenatal APRPD higher than 15 mmm and VUR (32). Similarly, Passerotti et al. found a significant association between the degree of postnatal hydronephrosis and VUR (3). Other postnatal US findings associated with VUR are renal parenchyma thinning [Odds Ratio (OR) 2.94], ureteral dilation (OR 1.52) and duplication (OR 2.42) (3). In contrast, in a systematic review, Passerotti et al. have not found an association between the degree of postnatal hydronephrosis and VUR (3). The aim of the treatment of VUR is avoidance of kidney damage and UTI, but surgical procedure did not change the number of UTI and kidney damage (76, 77). Therefore, surgical intervention is not necessary in most cases of VUR, because spontaneous resolution occurs in the majority of cases (78-80). Furthermore, children with antenatal diagnosis of VUR have a resolution rate higher than VUR diagnosed after febrile UTI (78).

Table 3 resumes studies about APRPD and VUR.

Table 3

Primary obstructive megaureter (POM)

The primary obstructive megaureter (POM) has an incidence of 1.8/1000 births and affects more boys than girls and the left side (7, 81-83). It is defined as an ureteric diameter equals or superior to 7 mm (84). It can be associated with another CAKUT and malformations (81). The urological abnormalities associated are UPJO, renal hypo-/dysplasia, VUR and renal agenesis (81). The most common symptoms are UTI and abdominal pain (81, 83, 85, 86).

Concerning US findings, Gimpel et al. have not found an association of the degree of hydronephrosis with the width of megaureter (81). They found spontaneous resolution in megaureters with a diameter less than 8.5 mm (81). Notwithstanding, Passerotti el al. found a significant association of renal pelvic dilatation, ureteral duplication (OR 4.54) and megaureter (OR 27.60) with POM (3).

DRS findings vary from normal, dilated non-obstructive, partial obstruction and obstructive pattern (81). Poor drainage alone is not a predictor of surgery, since it can be consequence of full bladder or the effect of gravity (84).

The majority of cases are non-surgically managed (81, 83, 84). A combination of clinical and radiological findings must be taken into account for the decision of the best management (84). Surgery is indicated when there are repetitive UTI, abdominal pain, impairment of renal function (presence of an initial DRF below 40% or a drop of 5% on serial scans), severe hydroureteronephrosis and/or increased dilation (81, 82, 84, 85, 87). The rate of surgery varies between 20-30% in the literature (81, 83, 88). According to Chertin et al., independent risk factors for surgical procedure were SFU grade 3-4 of postnatal hydronephrosis, DRF less than 30% and ureteral diameter more than 13.3 mm (88). Others predictors related to spontaneous resolution are perinatal presentation and non-obstructive washout pattern (83). Recently, Di Renzo et al. prospectively studied 57 children with antenatally diagnosed POM and, during the first year of life, they found very low frequency of surgery (86). This finding supports the evidence for non-surgical treatment mostly to patients with early diagnosis. Nevertheless, long-term follow-up of non-surgically managed megaureters is warranted due to evidence of late symptoms in adolescents and adults (84).

Therefore, it has been clearly showed that many children with partial ureterovesical junction obstruction will also spontaneously resolve their hydronephrosis (86). Recently, the British Association of Paediatric Urologists reported a consensus statement on the management of the primary obstructive megaureter and recommended initial non-surgical management. Indications for surgical intervention include an initial DRF < 40% and complications related to non-surgical management (84).

Posterior urethral valve (PUV)

PUV is a common cause of lower urinary tract obstruction in male infants with a reported incidence of 1 in 3000 to 1 in 8000 boys (89-93). PUV is also a common cause of CKD in children (89-93). PUV is commonly associated with kidney dysplasia, bladder dysfunction, VUR and Prune Belly syndrome (94, 95).

Heikkila et al. found an incidence of ESRD in 22.8% among 193 patients with PUV (96). Smith et al. evaluated the long-term outcome of 100 patients treated for PUV and found that 10% had ESRD by 10 years of age, and 38% required dialysis by 20 years of age. Chronic renal disease was present in 34% and 51% at 10 and 20 years of age, respectively (97). Ansari et al. studied 260 boys and found an incidence of 11.8% of ESRD at a mean age of 11.2 years (92).

The most common symptoms are a palpably distended bladder or upper urinary tract, ascites, respiratory distress or sepsis in neonates and UTI and bladder dysfunction in older children (91, 95, 97, 98).

The VCUG is the gold standard test for the diagnosis of PUV with typical findings of a dilated prostatic urethra, bladder trabeculation, and a narrow bladder neck. Overall, 50% of patients with PUV have VUR, being half of them bilateral (95, 98, 99).

Furthermore, the most common US findings are hypertrophied bladder, increased kidney echogenicity and severe urinary tract dilatation (3, 7). In a systemic review, thickened bladder was almost 25 times and kidney hyperechogenicity was 7.5 times significantly associated to PUV(3). Renal scintigraphy with DMSA is important to evaluate renal damage and to provide a baseline for follow-up and prognosis.

The management of PUV is always surgical intervention, but this can be done at the antenatal or postnatal period (98). Antenatal management remains controversial and comprises early delivery, vesico-amniotic shunting, open fetal surgery and percutaneous fetal cystoscopy (98). Regarding postnatal treatment, it is primarily focused on relief of the bladder outlet obstruction by endoscopic valve ablation; alternative initial treatments include temporary cutaneous vesicostomy or high urinary diversion (95, 97). Valve ablation is the treatment of choice (97, 100). If the urethra is too small for the cystoscope, vesicostomy is recommended (101). There is no benefit to high diversion with cutaneous pyelostomy over primary valve ablation, and the latter is reserved for patients who have persistent severe hydronephrosis and renal dysfunction after valve ablation (97, 102, 103).

The rate of urinary incontinence in these patients ranges from 19% to 81% (92, 98). Whereas not all patients with dysfunctional bladders have incontinence, all patients with incontinence have dysfunctional bladders, which are found in up to 75% of all patients following valve ablation (98)

Multicystic dysplastic kidney (MCDK)

The MCDK has an incidence of 1/4300 - 2.1/1000 births with male predominance (5, 7, 23, 104). Among patients with antenatal urinary tract abnormalities, it corresponds 4 to 6% of total (1, 10). It is usually unilateral and if bilateral is incompatible with life (23). About histological findings, MCDK is defined as a structural disorganization of renal tissue with undifferentiated epithelium and

primitive ducts surrounded by fibromuscular connective tissue, being the kidney entirely or partially involved with grossly visible cysts (105). The principal urinary tract anomalies associated are VUR, UPJO and UVJO (104, 106-110). Some rare complications reported in the literature are UTI, hypertension, CKD and neoplasia (106, 111).

The most common image exams for MCDK are US and DMSA radioisotope scan. On radioisotope scan, generally, there is no kidney function (23). Serial renal ultrasonographies show a tendency of involution of the affected kidney (109, 110, 112, 113). VCUG and dynamic radioisotope scan are recommended only if there is some alterations on the contralateral kidney (114).

The main indications for surgery are large mass compromising breathing or feeding, hypertension and no involution of the kidney (23, 105, 108, 109, 112). Nowadays, MCDK is non-surgically managed, since the complications are rare and the involution of the affected kidney frequently occurs (104, 106, 109, 110, 113, 114). Eickmeyer et al. found a cumulative probability of involution of 9.8% at one year of age, 38.5% at five years of age, 53.5% at ten years of age and 64.9% at 15 years of age (112). Similarly, Tiryaki et al. reported an involution of 33% at 3 years of age (109) and Rabelo et al. detected that 75% of the MCDK was below 5^{th} percentile at 36 months of age (113).

Hypertension is a rare event and its incidence is about 3-5% (112, 113). Chiappinelli et al. retrospectively studied non-surgically treated patients from 6 months to 11 years of follow-up and none of them developed hypertension (76). Recently, a Canadian guideline suggests nephrectomy in case of uncontrolled hypertension. Children with MCDK must be followed up in order to detect hypertension and proteinuria secondary to hyperfiltration (114). However, there are only some case reports and case series about the control of hypertension after nephrectomy (111, 115-117). Some cases of hypertension are associated to abnormalities of the contralateral kidney or other comorbid (106, 112).

In regard to malignancies, the occurrence is extremely rare (104, 105). This is one of the reasons that supports the non-surgically treatment (104, 105). Mattiolli et al. and Chiappinelli et al. did not detected malignancies in their studies (105).

Nevertheless, there are some cases of Wilms tumor or nephroma related with MCDK (118, 119).

Concluding remarks

In summary, CAKUT are a heterogeneous and complex group of diseases responsible for UTI, CKD and hypertension in children. CAKUT are responsible for 20 to 30% of all prenatally detected anomalies. These anomalies are the most common cause of CKD in childhood (120). A multidisciplinary team approach is required to diagnose and treat these complex disorders. Future risk factors will likely include urinary or serum biomarkers, more quantitative analysis of hydronephrosis patterns and less invasive functional imaging modalities such as MRI to predict outcome in a more accurate manner. The long-term impact of the precocious management of these renal abnormalities also needs to be addressed by future prospective studies with significant clinical outcomes including proteinuria, hypertension, and CKD (121, 122). Despite the evolution in imaging exams and biomarkers, there has not been so far a gold standard exam to define surgical treatment. The definition of the best time and which patients will need surgery is still a matter of debate for nephrologists and urologists. Nevertheless, the natural history of CAKUT has shown that the best management in most cases is non-surgical. Currently, non-surgical management of CAKUT should be considered whenever possible for infants with ANH (11, 123).

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Table 1 – Antenatal hydronephrosis and risk of renal pathology

Source	Period	Studied population (N)	Conclusions
Lee et al (2)	1983-2003	Patients with antenatal hydronephrosis (1308 patients)	The risk of any postnatal pathology per degree of antenatal hydronephrosis was 11.9% for mild, 45.1% for moderate, and 88.3% for severe.
Blachar et al (35)	1987 -1991	Patients with antenatal pelvic-to- renal APD ratio greater than 0.35 (69 patients)	APRPD of 9 mm or more, and a pelvic-to-renal APD ratio of 0.45 before 32 weeks of gestation and 0.52 thereafter, were found to be useful for the detection of severe outcome.
Chertin et al (34)	1988-2003	Patients with antenatal hydronephrosis (343 patients)	Surgical correction was needed in 179 children (52.2%) during the course of conservative management. SFU grade 3–4 of postnatal hydronephrosis was an independently predictor factor for surgery.
Passerotti et al (6)	1998-2006	Patients with antenatal hydronephrosis ≥ 8mm in the third trimester (1441 children)	On multivariate analysis, the degree of hydronephrosis in the first postnatal ultrasound was correlated with an increased risk of 'any' urological pathology.
De Kort et al (32)	2000-2005	Patients with antenatal hydronephrosis ≥ 5 mm (125 patients)	Infants with fetal APRPD ≥15 mm require significantly more surgical interventions than infants with fetal APRPD <15 mm.
Barbosa et al (33)	2002-2006	Patients with antenatal hydronephrosis ≥ 5 mm in third trimester (329 patients)	Most mild cases resolved spontaneously, a quarter of moderate and more than half of severe cases required surgery.
Plevani et al (11)	2002-2007	Patients with antenatal hydronephrosis ≥ 5 mm in third trimester (120 fetuses)	The rates of postnatal urinary tract pathology were 14, 27 and 53% for antenatal HY of ≤ 7, 8 – 15 and > 15 mm, respectively. An APRPD ≥ 7 mm in the third trimester had a sensitivity of 100% and a specificity of 23% to predict unfavorable outcome. For absent urinary tract anomalies and APDRP < 15 mm, there is a < 10% chance that postnatal surgery will be needed.
Rianthavorn et al (38)	2007-2012	Full-term infants with antenatal hydronephrosis. Postnatal APRPD ≥ 10 mm or SFU grade 3-4 in the neonatal ultrasound (96 newborns)	Areas under the receiver operating characteristic plots (95 % CI) were 0.86 (0.79–0.94) versus 0.81 (0.73–0.89); p = 0.08, and 87.6 versus 79.8 % of cases were correctly classified, for APRPD ≥ 16 mm versus SFU grade 4, respectively.

APRPD – anteroposterior renal pelvis diameter; SFU - Society of Fetal Urology; APD – anteroposterior diameter

Table 2 – Predictors of need of surgery in patients with ureteric pelvic junction obstruction

Source	Period	Studied population (N)	Predictors	Conclusions
Arora et al (53)	2004-2012	Antenatally detected hydronephrosis due UPJO (109 renal units)	Initial postnatal APRPD and pre-operative DRF	APRPD>24.3mm (sensitivity 73.1% and specificity 88%)
Longpre et al (59)	-	Antenatally detected hydronephrosis (100 patients - 118 renal units)	Initial postnatal APRPD and SFU 4	Mean initial APRPD in surgical group was 29 mm
Mudrik-Zohar et al (54)	2001-2012	Antenatally detected isolated hydronephrosis due UPJO (69 patients)	Antenatal APRPD of third trimester and APRPD/PT ratio	- Antenatal APRPD > 14 mm, (AUC 0.817 – sensitivity 77% and specificity 69%) APRPD/PT ratio > 2.1 (AUC 0.822 – sensitivity 87% and specificity 65%)
Dias et al (37)	1999-2010	Antenatally detected isolated hydronephrosis due UPJO (312 patients)	Antenatal and initial postnatal APRPD	- Antenatal APRPD > 18 mm (AUC 0.96 – sensitivity 92 % and specificity 89.5%) - Postnatal APRPD > 16 mm (AUC 0.97 – sensitivity 99.8% and specificity 88.5%)
Chertin et al (34)	1988-2003	Antenatally detected hydronephrosis due UPJO (343 patients)	Postnatal SFU grade 3-4 and DRF	SFU grade 3-4 and DRF < 40% were independently predictive factors for surgery

APRPD = anteroposterior renal pelvis diameter; SFU = Society of fetal urology; PT = parenchymal thickness; AUC = area under the curve

Table 3 – Association between anteroposterior renal pelvis diameter and vesicoureteral reflux

Source	Period	Studied population (N)	Conclusions
Lee et al (2)	1983-2003	Patients with antenatal hydronephrosis (1308 patients)	No association between the grade of ANH and the risk of VUR
Passerotti et al (6)	1998-2006	Patients with antenatal hydronephrosis ≥ 8mm in the third trimester (1441 children)	Significant association between the degree of postnatal hydronephrosis and VUR.
De Kort et al (32)	2000-2005	Patients with antenatal hydronephrosis ≥ 5 mm (125 patients)	There is an association between antenatal APRDP higher than 15mm and VUR
Dias et al (41)	1999-2008	Patients with isolated antenatal hydronephrosis ≥ 5 mm (250 patients)	Fetal and postnatal renal pelvic dilatation were poor predictors of VUR. On the other hand, they found that fetal and postnatal renal pelvic diameter less than 10 mm make the diagnosis of VUR improbable.

APRPD – anteroposterior renal pelvis diameter; VUR – vesicoureteral reflux

2.2. Artigo de revisão II

Management and clinical outcomes of posterior urethral valves

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Abstract

Lower urinary tract obstruction (LUTO) comprises a heterogeneous group of pathologies, commonly causing bladder neck obstruction. Posterior urethral valves (PUV) constitute the most common infravesical urinary obstruction in boys. PUV are often accompanied by severe consequences to the lower and upper urinary tract and are the most common cause of end stage renal disease (ESRD) during childhood. In spite of continuous advances in the diagnosis and management of patients with PUV in the last decades, approximately a quarter of the patients present progression to ESRD during a long-term follow up. In addition, besides renal function impairment, patients with PUV can also exhibit multiple associated morbidity that extends beyond childhood through adolescence and into adult life.

Keywords: Posterior urethral valves - urinary tract obstruction – antenatal diagnosis – antenatal intervention - chronic kidney disease

Introduction

Congenital anomalies of kidney and urinary tract (CAKUT) comprise a complex spectrum of anomalies that can occur at the level of the kidney, collecting system, bladder, or urethra{1}. Over the past 20 years, there has been a continuous advance in the understanding of genetic basis and clinical course of CAKUT {2,3}. Congenital kidney and urological disorders account for up to 60% of chronic kidney disease (CKD) in infants and they are the most common cause of end stage renal disease (ESRD) in this age group {4,5}.

Among CAKUT disorders, lower urinary tract obstruction (LUTO) represents the most severe obstruction of the urinary tract that can be antenatally recognized. LUTO is relatively rare but can result in substantial perinatal mortality with lifelong morbidity {6-8}. Posterior urethral valves (PUV) constitute the most common infravesical urinary obstruction in boys. PUV are often accompanied by severe consequences to the lower and upper urinary tract{9,10}. Among CAKUT disorders, PUV are the most common cause of ESRD during childhood {11}. In spite of continuous advances in the diagnosis and management of patients with PUV in the last decades, approximately a quarter of the patients present progression to ESRD during a long-term follow up{12}. In addition, besides renal function impairment, patients with PUV can also exhibit

associated morbidity that extends beyond childhood through adolescence and into adult life {13,14}. PUV are associated with recurrent urinary tract infection (UTI), dysfunctional voiding, urinary incontinence, and CKD. The current literature about PUV lacks a systematic analysis of these clinical outcomes, which might provide further insight into unresolved issues. The aim of this review is to provide an overview of the current advances in the management and in the clinical outcomes of children with PUV.

Epidemiology and Etiology

Congenital LUTO is a relatively rare event affecting primarily male fetus. A population-based registry study from the United Kingdom Northern Region has shown that LUTO has an incidence of 2.2 per 10 000 births. Between 1984 and 1997, 113 cases were registered, with the underlying pathology identified by postnatal investigation or autopsy. In this study, the incidence of PUV was 1.4/10 000 births [{15}].

Recent epidemiological data suggest that the birth prevalence of LUTO is stable. In a large population-based study from United Kingdom, there were 284 LUTO cases in 851 419 births during the study period, representing a total prevalence of 3.34 (2.95–3.72) per 10 000 births. This prevalence did not change significantly between 1995 and 2007 [{16}].

Posterior urethral valves are the most common congenital obstructive lesion of the urethra, with an estimated incidence of 1 per 3,000 to 8,000 live birth [{17}]. PUV are a relatively rare disorder, with a disproportionately elevated incidence in African-Americans and infants with Down's syndrome[{18}]. Lloyd et al.[{19}] reported, using the Kids' Inpatient Database (KID), a national database of several million inpatient pediatric hospitalizations per year that a total of 578 newborn males were diagnosed with PUVs from 1997 to 2009 in USA. According to this database, there was a weighted prevalence rate of 9.3 PUV births per 100,000 in-hospital live male births. There was no significant change in the birth prevalence of PUV in newborn males during the study period. Newborns with PUV were more commonly black and less commonly white, Hispanic or Asian/Pacific Islander ($p < 0.001$). Similarly, in the population-based study from United Kingdom [{16}], the prevalence of LUTO was significantly higher in black and minority ethnic groups when compared with white Europeans (OR 2.38; 95% CI 1.87–3.03), and are associated with area-based deprivation measures ($P < 0.01$). Clearly, it is important to notice the impact of prenatal

ultrasound on epidemiology of the major genitourinary malformations. For instance, Cromie et al.[20] evaluated the database from the Malformations Surveillance Program at Brigham and Women's Hospital between 1974 and 1994, including data tracked of 163,431 pregnancies and pregnancy termination rates of fetuses with spina bifida, bladder exstrophy, the prune belly syndrome and PUV. Pregnancy was electively terminated in 65% for spina bifida, 25% for bladder exstrophy, 31% for the Prune Belly syndrome and 46% for PUV. Interestingly, the rate of pregnancy terminations began to increase after 1982 and accelerated after 1986 concomitantly with improvements in antenatal sonography.

PUV is most commonly sporadic, however familial cases have been reported. For instance, there have been described in two successive generations[21], in two siblings [22,23], in three siblings [24]and in identical and nonidentical twins [25,26]. These findings suggest that genetic factors may play a role in the origins of PUV. Recently, Boghossian et al. [27] have shown a potential role of copy number variations (CNVs) in up to 57% of cases of PUV examined. Investigation of genes in these CNVs may provide further insights into genetic variants that contribute to PUV.

Anatomically, PUV are obstructing membranous folds within the lumen of the posterior urethra and the obstruction resulting from valve leaflets or a membranous diaphragm situated at the distal limit of the verumontanum, the prominent mound of prostate tissue that forms an anatomical feature in the floor of the normal posterior urethra[9,10,17,28]. The etiology of PUV remains elusive and the precise origins regarding the anatomy and embryology of posterior urethral valves remain undefined. Historically, Tolmatschew [29] was the first to postulate an embryological theory of PUV development, namely overgrowth of normally present urethral folds. Young et al. [30] published in 1919 a landmark article in the history of PUV. They described the largest series at that time including clinical presentation, diagnosis, intervention and autopsy in 12 infants with PUV. Of note, they were the first to classify valves into types 1 to 3. Since that original classification, the description of PUV embryology has weaving between claims of abnormal integration of the Wolffian ducts into the urethra and exaggerations of normal folds seen in normal urethral development [17,18].

Contemporarily, studies on the topic claims that the term valves was incorrect because the condition actually reflected obstruction in the posterior urethra caused by a single membrane and Type I and II valves represent the same entity. Dewan et al. [31-34]

in series of papers in the early 1990s proposed the term COPUM (congenitally obstructing posterior urethral membrane) to take the place of the more classic term PUV. They believed that there were only two distinct entities with two distinct embryological origins causing obstruction in the posterior urethra, namely COPUM and Cobb's collar. The term "Cobb's collar" has been applied to a distinct congenital urethral stricture occurring distal to an external urethral sphincter. Modern studies using three-dimensional reconstruction of the histological images study supports the concept of a persistent urogenital membrane, as the etiology of PUVs [17]. Nevertheless, the embryology of PUV is far from clear and currently is an area fertile for research[35].

Diagnosis

On antenatal sonography, the constellation of findings most consistent with fetal LUTO includes male gender, bilateral hydronephrosis, enlargement of the fetal bladder (megacystis), a dilated posterior urethra (keyhole sign), and oligohydramnios [6,36]. Therefore, an antenatal US typically reveals bilateral hydronephrosis with a distended and thickened bladder, dilated prostatic urethra and hypertrophic bladder neck. Nevertheless, the spectrum of findings is varied: a combination of bilateral hydroureteronephrosis, bladder distention, cortical thinning, cortical cysts and oligohydramnios can be observed depending on obstruction severity. In the prenatal setting, specific sonographic criteria such as bladder wall thickening and dilated posterior urethra are somewhat difficult to identify [37, 38]. The earliest sign of LUTO is the presence of megacystis (distension of the fetal bladder) which could be diagnosed as early as 11 weeks. Bladder diameters greater than 17 mm in the first trimester is most likely caused by obstructive disorders [39]. In the second trimester, megacystis has been defined as an abnormally large appearing bladder, with or without the failure of the bladder to empty over 45 mins[40]. PUV are the most frequent cause of megacystis detected in the second or third trimester [41-43]. The presence of oligohydramnios is frequently associated with bladder outlet obstruction and its observation is also a sign of poor prognosis [44-47]. In a series of 40 cases of urethral obstruction, Mahony et al. [48] showed that decreased amniotic fluid volume was present in 52.5% of the cases and 80% of them did not survive. Bladder distention was observed in 90% of the cases and 88% of them had a poor prognosis.

Distinguishing between the different causes of LUTO is challenging given the overlap in sonographic characteristics [6]. PUV is the principal cause and the other

causes must be included in the differential diagnosis are urethral atresia, prune belly syndrome, anterior urethral valves/anterior urethral diverticulum, congenital megalourethra, and obstructing ureteroceles.

Posterior urethral valves have a wide range of clinical presentations. Currently, antenatal ultrasound evaluation of the developing fetus has become routine care in the management of healthy pregnancies. Consequently, kidney and urinary tract abnormalities, including PUV have been diagnosed in utero [49,50]. Two-thirds of infants with PUV have been identified by prenatal US in the last years in the developed world[51]. The scenario in the developing world is remarkably different [52,53]. Before the era of antenatal detection, the majority of infants with PUV were identified in the first year of life with a combination of symptoms and signs such as poor urinary stream, distended bladder, failure to thrive, and UTI. Neonates may occasionally present with abdominal distension, abdominal mass, poor urinary stream and respiratory distress due to pulmonary hypoplasia [9,54,55]. These children frequently presented also with septicemia, acidosis and at various stages of CKD [56]. Although most patients are diagnosed in the prenatal and neonatal period, there have been published reports regarding patients presenting in adolescence and the second decade of life[57]. Among the most common symptoms in late presenting PUV are voiding symptoms, incontinence, hematuria and UTI [58,59]. In adults, voiding and ejaculatory dysfunction have been reported as predominant symptoms [60,61].

Some studies have observed that some findings could increase the sensitivity of sonography in predicting urethral obstruction in the prenatal setting. Kaefer et al. [37] evaluated 15 male fetuses with a distended bladder and bilateral hydroureteronephrosis. Postnatally, 8 neonates were confirmed to have PUV. They demonstrated that the simultaneous presence of oligohydramnios and increased renal echogenicity was highly predictive of infravesical obstruction with 100% sensitivity and 93% specificity. Montemarano et al.[40] reported as most suggestive of PUV the presence of oligohydramnios, progressive bladder thickening and a dilated posterior urethra. Oliveira et al.[62] have shown in a cohort of 148 cases of fetal hydronephrosis (10% of LUTO), that after adjustment by multiple logistic regression analysis, two findings were identified as independent predictors of fetal urethral obstruction: oligohydramnios and megacystis. The sensitivity and specificity of the combination of both variables were 60 and 98.5%, respectively. Bernades et al.[63].demonstrated in a series of 42

fetuses suspected to have PUV, that increased bladder wall thickness and bladder dilatation were highly associated with the diagnosis of PUV ($P < 0.001$). However, a thick-walled bladder was observed in 39% and a dilated bladder in 48% of the infants with other pathologies than PUV.

Postnatally, the diagnosis of PUV is confirmed by a combination of renal imaging, including a prompt neonatal ultrasound and voiding cystourethrogram (VCUG). Renal-bladder US is an important tool to evaluate for the degree of hydroureteronephrosis, renal parenchyma, renal size, and bladder wall thickening. An increased renal echogenicity and subcortical cysts are poor prognostic signs for renal function [{64}]. A thick walled bladder may signify a poorly compliant bladder that can result in damage to the renal parenchyma and upper urinary tract at filling pressures above 40 cm H2O. A VCUG is absolutely indicated as an immediate postnatal study for neonates with suspected bladder outlet obstruction, most commonly PUV [{6}]. A thick-walled trabeculated bladder, bladder diverticulum and vesicoureteral reflux (VUR) are also frequent[{38}]. Nevertheless, in a systematic review on the accuracy of diagnostic procedures for infravesical obstruction in boys, Hennus et al.[{65}] were unable to draw conclusions on diagnostic accuracy of tests as a consequence of low quality of methods of the available studies.

Management

Antenatal sonography has allowed the early detection of a broad spectrum of structural anomalies. Advance warning of these conditions has radically altered neonatal practice concerning diverse aspects including medical and ethical issues. In case of a severe obstructive uropathy is suspected, multidisciplinary counselling should be offered immediately. The diagnosis and management of complex CAKUT require a team effort, because no single specialty is fully equipped to deal with all the maternal and fetal implications of a diagnosis of a structural defect. Prenatal diagnosis of these anomalies provides a unique opportunity to influence perinatal management favorably. Therefore, the medical team must plan the optimal fetal and neonatal care of fetuses with a prenatally-diagnosed severe malformation. Nevertheless, some challenging clinical aspects must be addressed by the medical team including parental counselling, site of delivery for immediate postnatal treatment, possible early delivery to prevent ongoing fetal organ damage, intervention in utero to prevent, reverse, or minimize fetal organ injury or death, and even pregnancy termination[{66,67}].

Antenatal intervention

The foundation upon which fetal intervention for LUTO is based on animal studies suggesting that earlier reversing of the fetal urethral obstruction can preserve renal function, resulting in improved amniotic fluid levels and allowing a subsequent pulmonary maturation[68,69]. Therefore, these assumptions have set the way for interventions attempting to decompress human fetal urinary tract obstruction and thus possibly improve prognosis and survival [70,71].

Ultrasound-guided percutaneous vesico-amniotic shunting (VAS) is the most commonly used method to relieve urinary tract obstruction [72]. This procedure was first reported in 1982 by Golbus et al[73] and the technique involves the placement of a double pig-tailed catheter under ultrasound guidance and local anaesthesia, with the distal end in the fetal bladder and the proximal end in the amniotic cavity to allow drainage of fetal urine. However, in spite of initial enthusiasm its efficacy is still debatable. In 1986, Manning et al.[74] reported, based on the International Fetal Surgery Register, the outcome of 73 fetuses with ultrasound evidence of LUTO that had been treated with VAS. Overall survival rates of 41% were demonstrated. Similarly, in 1997 Coplen [75] reviewed 169 cases of successful VAS placements over 14 years. Overall survival was found to be 47%, with 40% of survivors presented early ESRD. These studies suggested that better patient selection through further prognostic testing prior to intervention could further improve survival rates. In 2003, Clark et al.[76] conducted a meta-analysis to estimate the effect of prenatal bladder drainage on perinatal survival in fetuses with LUTO. The review identified 16 observational studies that included 147 fetuses and seven controlled series with 197 fetuses. Meta-analysis results showed that VAS appeared to improve overall perinatal survival as compared to the non-drainage group (OR = 2.5; 95% CI 1.0-5.9; $P < 0.03$). Interestingly, subgroup analysis indicated that this improved survival was predominantly noted in fetuses with a poor prognosis, defined on ultrasound appearance and/or fetal urinalysis basis (OR 8.0; 95% CI, 1.2-52.9; $P < 0.03$). The study concluded that, despite this form of fetal therapy having been practised for more than 25 years, there is a lack of high-quality evidence to reliably inform clinical practice[77]. Based on the findings of these studies, in 2005 was founded a randomized controlled trial (Percutaneous Shunting in Lower Urinary Tract Obstruction, PLUTO) to assess the short- and long-term effects of this intervention [7,78,79]. Unfortunately, the trial stopped early with 31 women randomised because of difficulties in recruitment. Morris et al.[72] reported that, based on intention-

to-treat analysis, survival at 28 days was higher in VAS arm (50%) than conservative management (27%) [relative risk (RR) 1.88, 95% confidence interval (CI) 0.71 to 4.96, p = 0.27]. At 12 months survival was 44% in the VAS arm and 20% in the conservative arm (RR 2.19, 95% CI 0.69 to 6.94, p = 0.25). Bayesian analysis suggested an 86% probability that VAS increased survival at 28 days and a 25% probability that it had a clinically important effect.

Fetal cystoscopy has been proposed as an alternative option to the VAS for severe LUTO with the advantage of providing a prenatal diagnosis and specific treatment of cause of bladder outlet obstruction. Sananes et al.[{80}] reported a retrospective cohort study of all fetuses that underwent cystoscopy for prenatal diagnosis of LUTO in three tertiary referral centers. A total of 50 fetal cystoscopies were performed revealing PUV in 31 (62%) fetuses. Among the infants, 17/30 (56.7%) survived and 13/17 (76.5%) had normal renal function at one year of life. Recently, Ruano et al.[{81}] presented a single center experience of a standardized prenatal multidisciplinary management protocol for fetal LUTO and proposed a classification based on disease severity. In a multivariate analysis, fetal intervention (OR 6.97 [0.88-70.16], Pr (OR>1)=96.7%), anhydramnios (OR 0.12 [0.04-0.35], Pr (OR<1)=99.9%), and favourable fetal urine analysis (OR 3.98 [0.63-25.15], Pr (OR>1)=92.7%) were predictors of survival.

Postnatal management and intervention

As mentioned earlier, an important benefit from prenatal diagnosis is the possibility of delivery in a tertiary care setting to facilitate the postnatal management. Neonates must be assessed by a multidisciplinary team including neonatologists, paediatric nephrologists and paediatric urologists. The initial assessment should include a thorough examination looking for abdominal masses and for signs such as respiratory distress, deficient abdominal wall musculature or undescended testes[{9,10}]. The early management of neonates suspected of LUTO can frequently require intensive care, in particular respiratory support. Bladder drainage is usually established by urethral catheter. Diagnosis and prompt correction of fluid, electrolyte, and acid-base imbalance are crucial. Infants presenting with urosepsis require, in addition to the adequate bladder drainage (urethral or suprapubic catheterization), appropriate systemic antibiotics. Renal function is estimated by measuring serum creatinine, and electrolyte and acid-base balance must be monitored frequently [{18,38}]. Hyperkalemic acidosis is a

known common serious sequela [82]. Microscopic examination and culture of urine are routine. Renal-bladder ultrasound and VCUG are normally arranged after clinical stabilization. Renal scintigraphy with DMSA is important to evaluate renal damage and provide a baseline for follow-up and prognosis. In neonates this is usually delayed for 4–6 weeks to allow for renal maturation.

The surgical management of PUV is undertaken after satisfactory preoperative control of metabolic issues and of infection. Currently, in developed countries the surgical management has been simplified by the introduction of miniaturized endoscopes. Therefore, the standard of care is the insertion of the catheter drainage until clinical stabilization, followed by transurethral ablation of the valves using the small resectoscopes now available to urologists [9,18,83-85]. Due to the improvement of these devices, most children can be ablated shortly after birth, with vesicostomies only required if the urethra will not allow for the passage of the resectoscope. It is beyond the scope of this review to explore the technical aspects of the diverse surgical procedures for PUVs.

Outcomes

All children born with PUV require long-term careful monitoring. The morbidity associated with PUV extends beyond childhood through adolescence and into adult life. The morbidity of PUV is related to the congenital obstruction of the urinary tract at a critical time in organogenesis which may have a profound and lifelong impact on kidney, ureter, and bladder function [83,86].

The mortality rate in patients with PUV has significantly decreased in the past decades, from 50% to less than 5% [55,87,88]. Survival rate has improved due to early diagnosis, improvement of respiratory support, and adequate management of renal function impairment in neonates and infants. In spite of these improvements in early management, long-term morbidity related to PUV still represents a heavy burden for these patients and for the medical team[13,14,38,89]. Jalkanen et al.[90] investigated the quality of life of men who had been treated for PUVs in childhood. The adult PUVs patients reported lower scores in sleeping, eating, and sexual activity. The PUVs patients with renal insufficiency or urinary incontinence had impaired quality of life in several dimensions

Therefore, with the advances in diagnosis and management, more patients have been facing the long-term sequelae of PUV during puberty and adulthood, including renal function impairment, bladder dysfunction, incontinence, and impaired sexual and reproductive functions[12,84,91].

Obstructive uropathy secondary to PUV is still a common cause of CKD disease in children. The rate of progression to CKD or ESRD has been reported from 22% to 68% [88,92-94]. Ylinen et al.[95] have shown in a series of 46 boys that the long-term renal outcome was poor in 14 (30%) after a mean follow-up period of 12.5 years. Interestingly, the highest rates of ESRD occurred in the first year of life and late adolescence, as shown similarly by an earliest study by Smith et al.[96]. By contrast, Heikkilä et al[12] have shown, from a large cohort with a long term follow-up of 193 patients, that 44 (22.8%) had progression to ESRD. According to Kaplan-Meier analysis, the lifetime risk of ESRD in this series was 28.5%. Of note, in this series a third of ESRD cases presented after the age of 17 years. However, the progression curve was somewhat steeper during the first year of life and in adolescence.

A number of studies have been identified possible prognostic factors affecting the renal outcome in patients with PUV [97]. Some predictive factors have been associated with the development of ESRD, including oligohydramnios, baseline creatinine concentration, nadir serum creatinine after a period of decompression, need of ventilatory support, bilateral vesicoureteral reflux (VUR), delayed diagnosis, bladder dysfunction, delayed achievement of urinary continence, and break through urinary tract infections[4,38,93-95,98-104]. Recently, Pulido et al. [5]have shown that a reduced renal parenchymal area as observed on the first postnatal ultrasound is associated with an increased risk of ESRD during childhood. On the other hand, some factors such as unilateral VUR, large congenital bladder diverticula, and urinary extravasation are considered as protective factors[105]. VURD (posterior urethral valves, unilateral VUR, and renal dysplasia) syndrome was first identified in 1982 by Hoover and Duckett, and described in 1983 by Greenfield et al. It is defined as persistent unilateral VUR and renal dysplasia in boys with PUV [106,107]. It works like a pop-off mechanism that unilateral VUR would lead to dysplasia in the affected kidney while sparing the contralateral kidney, portending a potentially more favorable long-term prognosis for renal function. However, recently, Hoag et al didn`t found protective effect in their retrospective study[108].

Lower urinary tract symptoms is a common phenomenon in boys with PUVs[13,14,109]. Initial urodynamic studies performed after valve ablation have found bladder dysfunction in as many as 75% of patients[110]. The most frequent urodynamic patterns found are hyperactive bladder, poor compliance and myogenic failure [111,112]. Recently, Hennus et al. [65] reported a systematic review on renal and bladder dysfunction after endoscopic treatment of infravesical obstruction in boys. They found 17 studies that reported urodynamic evaluation after valve ablation. Urodynamic abnormalities were found in 55% of patients (0–72%). In seven studies, a decreased bladder capacity was found in 42% of boys, (14–60%). A mean of 29% (0–50%) boys had poor bladder compliance and 31% (0–64%) had detrusor overactivity. Hypocontractile bladder was seen in 35% (0–73%), reported in eight studies. Post voiding residual urine was found in 31% (0–56%) [41,113-120]. Transitory polyuria after valve ablation occurs in up to 60% of boys with PUVs as consequence of a defective renal concentrating ability.

Urodynamic abnormalities of the lower urinary tract without properly management through childhood can lead to progressive renal damage despite successful relief of bladder outlet obstruction [9,10,121,122]. Of note, to add further complexity, these bladder alterations can occur in sequence in same patients during childhood and adolescence. A detailed evaluation of the bladder dysfunction will help in planning the management and possibly improve the long-term outcome. Therefore, it is crucial to the management of these patients a follow-up with carefully clinical assessment of bladder voiding pattern, serial ultrasound examination, and urodynamic investigation. Infants with hyperreflexic bladders needs anticholinergic therapy, the small noncompliant bladders of childhood may need medical therapy as well as clean intermittent catheterization (CIC), while for the myogenic bladders of later childhood, CIC is often necessary[83]. Consequently, these children require multiple and sequential interventions including timed/double voiding, anticholinergics, and clean intermittent catheterization. In cases where conservative measures are not successful in protecting renal function, enterocystoplasty is required. Patients with increasing hydronephrosis, deteriorating renal function and a poorly compliant bladder that fails to respond to medical measures should undergo bladder augmentation. Ureteral, Ileal or colonic bowel segments are effective in providing capacity and compliance with emptying via urethral CIC or catheterization of a surgically created continent channel between the bladder and abdominal wall (Mitrofanoff procedure)[9,10,18,84]. Interestingly, Tikkinenet al.[91]

assessed the impact of childhood PUV on lower urinary tract symptoms in adulthood. Overall, at least one moderate or severe lower urinary tract symptom was reported by 32.4% of patients with PUVs urethral valves and 15.8% of controls ($p < 0.002$).

In addition to the concerns of the valve bladder syndrome on renal function, the valve bladder may also lead to incontinence, with as many as 17–70% of children complaining of wetting at advanced ages. Often patients with PUVs achieve continence at a delayed age, especially patients with unfavourable kidney outcome. The two main causes of this incontinence are bladder dysfunction and sphincter incompetence [88,120].

Few studies have addressed the sexual function and fertility in PUV patients. It has been suspected that fertility could be impaired in this population [13,14,124]. Moreover, CKD is a common long-term complication in these patients and it is well recognized that libido and potency are affected in adults with renal impairment. The posterior urethra can remain elongated and dilated in PUV patients, despite successful valve ablation. Bladder neck and sphincteric lesion may lead to retrograde ejaculation. Scarring of the posterior urethra secondary to valve ablation, reflux into the seminal vesicles and the ejaculatory ducts, and cryptorchidism, which has been referred as occurring on 16% of PUV patients [84].

Concluding remarks

Posterior urethral valves (PUV) are the most common cause of lower urinary tract obstruction in male infants. Currently, PUV are typically suspected based on prenatal sonography and the definitive diagnosis is made postnatally. The management of children with PUV is complex and requires a multidisciplinary team. Patients require long-term follow up after ablation of valves with careful monitoring of renal function and of signs of bladder dysfunction. An appropriate management may prevent further deleterious effects on the upper urinary tract and maintain renal function. Although prognosis has been improved in the past decades, patients born with PUVs are committed to nephrological and urological follow-up, from early life until adolescence and adulthood.

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Conflicts of interest

None

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3. OBJETIVOS

1- Avaliar os fatores clínicos, laboratoriais e de imagem preditores para intervenção cirúrgica com paciente com CAKUT.

2- Desenvolvimento de um modelo preditivo para necessidade de cirurgia em pacientes com CAKUT.

3- Análise de fatores preditivos para evolução de DRC moderada (estágio ≥ 3) e grave (estágio 5) em pacientes com VUP.

4- Desenvolvimento de modelo de predição para DRC moderada (estágio ≥ 3) em pacientes com VUP.

4. PACIENTES E MÉTODOS

4.1. ESTUDO MODELO DE PREDIÇÃO PARA INTERVECÃO CIRÚRGICA EM CAKUT

4.1.1. **PACIENTES:**

Todos os lactentes com o diagnóstico perinatal de CAKUT (n=819) admitidos na Unidade de Nefrologia Pediátrica do Hospital das Clínicas/UFMG de 1987 a 2013 foram acompanhados.

Foram registrados, em protocolo próprio, os dados clínicos, os exames laboratoriais e de imagem à admissão e durante toda a evolução, o tratamento e os dados evolutivos de cada paciente. Para o presente estudo, foi desenvolvido um banco de dados específico no programa *Statistical Package for the Social Sciences (SPSS)* versão 18.0.

- **Critérios de inclusão:** Crianças portadoras de nefrouropatias acompanhadas na Unidade de Nefrologia Pediátrica de 1987 a 2013.
- **Critérios de exclusão:**
  - Fetos com aneuploidias ou malformações múltiplas (n=10);
  - Pacientes que interromperam o acompanhamento logo após o nascimento

  (n= 115).

4.1.2. **DELINEAMENTO:**

O delineamento da pesquisa é de um estudo de coorte retrospectivo, sendo os dados coletados de pacientes acompanhados entre janeiro de 1987 e dezembro de 2013. Com a finalidade de atender os objetivos propostos foi feita a identificação de pontenciais fatores de risco que foram independentemente associados à necessidade de intervenção cirúrgica durante o período de seguimento e determinação de um modelo de predição clínica de necessidade de intervenção cirúrgica.

- **Desfecho clínico de interesse:** o desfecho clínico de interesse foi a necessidade de intervenção cirúrgica durante o seguimento.

- **Variáveis explicativas:** As seguintes variáveis foram incluídas na análise: gênero, idade a admissão no serviço, creatinina plasmática à admissão, ritmo de filtração glomerular estimado à admissão, presença de oligoidrâmnio na gestação, presença de outras alterações do trato urinário associadas, lateralidade da hidronefrose (unilateral versus bilateral), presença de lesões no DMSA (ausente, unilateral ou bilateral), diâmetro anteroposterior (DAP) da pelve renal à admissão e período do diagnóstico (1987 a 1999 versus 2000 a 2013).

4.1.3. PROTOCOLO CLÍNICO

- **Acompanhamento clínico:** Os dados clínicos dos pacientes foram registrados em protocolo próprio. O seguimento clínico foi indicado, inicialmente, para todas as crianças, tendo sido instituída antibioticoprofilaxia para infecção do trato urinário (ITU). A antibioticoprofilaxia foi instituída a todos os pacientes admitidos antes de 2009 e apenas para aqueles com DAP $\geq$ 10 mm admitidos após 2009. Utilizou-se a cefalosporina de primeira geração (cefalexina 50mg/dia) nos dois primeiros meses de vida. Após essa faixa etária, a profilaxia foi modificada para sulfametoxazol+trimetoprim (1-2mg/kg/dia de trimetoprim) ou nitrofurantoína (1-2mg/kg/dia) em dose única diária. A profilaxia foi mantida enquanto aguardava-se propedêutica de imagem, para casos de ITU de repetição, para aqueles com DAP $\geq$ 10 mm, para pacientes com uropatias até a correção cirúrgica e para pacientes com refluxo vesicoureteral (RVU) maior ou igual a 3.

  A cada retorno do paciente foram avaliados: crescimento pôndero-estatural, evolução clínica, pressão arterial sistêmica, adesão ao uso do medicamento antibacteriano profilático e quadro clínico - laboratorial de ITU (urina rotina e urocultura).

A avaliação da função renal (por meio da dosagem sérica de uréia, de creatinina e cálculo do ritmo de filtração glomerular estimado) foi obtida, semestralmente, no primeiro ano de seguimento e, após esse período, anualmente ou mais frequentemente, conforme a necessidade clínica.

A medida da pressão arterial sistêmica foi realizada em todas as consultas médicas, com a utilização de esfigomomanômetro de tamanho apropriado para a idade, como recomendado pelo *Working Group of the National High Blood Pressure*

Education Program. Foram considerados os valores de referência e definições empregadas no estudo da *FourthTask Force on Blood Pressure in Children (1)*.

- **Investigação por imagens:** A avaliação por imagens do trato urinário foi obtida em todos os neonatos com dilatação da pelve renal, de acordo com o algoritmo da figura 1 até o ano de 2009. Após 2009, a uretrocistografia miccional passou a ser realizada apenas em pacientes com DAP > 10 mm.

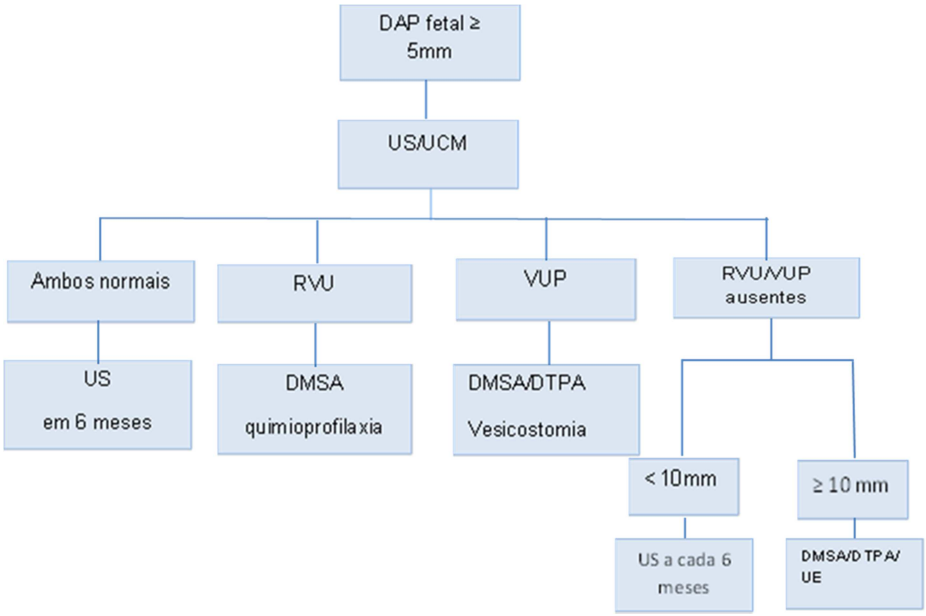

Figura 1 - Algoritmo para avaliação do trato urinário do neonato portador de hidronefrose fetal antes de 2009 (Oliveira, EA, Protocolo da Unidade de Nefrologia Pediátrica do HC/UFMG).

US: ultrassonografia; UCM: uretrocistografia miccional; RVU: refluxo vesicoureteral; VUP: válvula de uretra posterior; DMSA: cintilografia estática; DTPA: cintilografia dinâmica; UE: urografia excretora

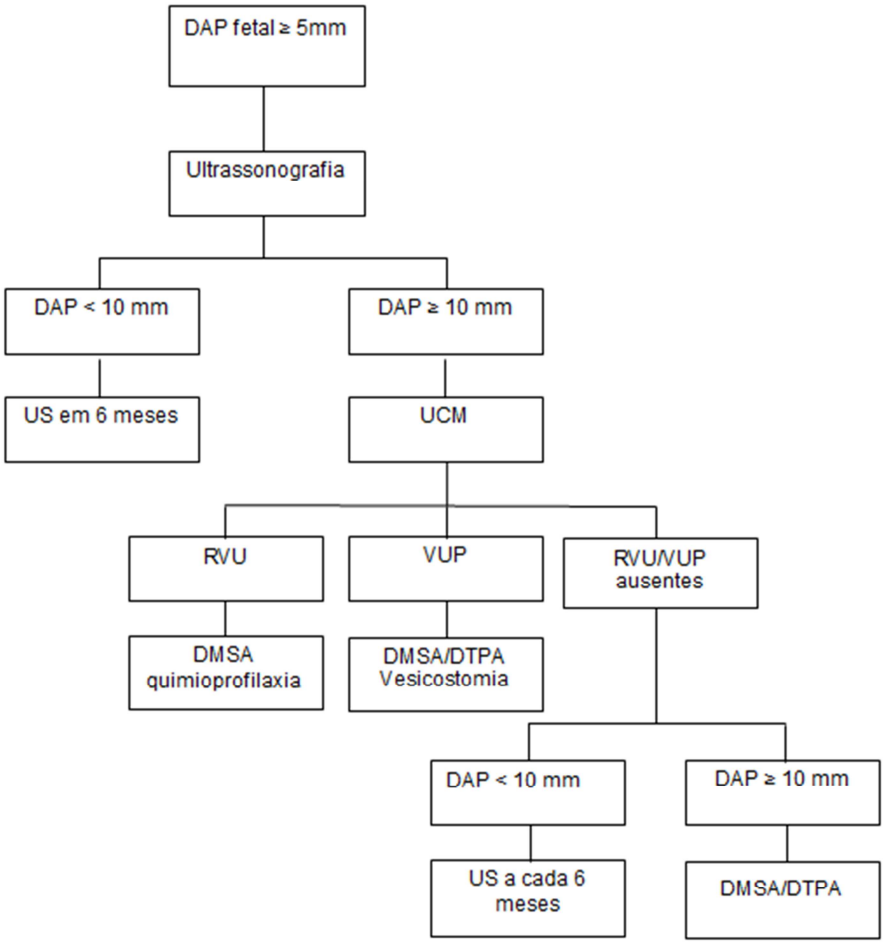

Figura 2 - Algoritmo para avaliação do trato urinário do neonato portador de hidronefrose fetal após de 2009 (Oliveira, EA, Protocolo da Unidade de Nefrologia Pediátrica do HC/UFMG).

US: ultrassonografia; UCM: uretrocistografia miccional; RVU: refluxo vesicoureteral; VUP: válvula de uretra posterior; DMSA: cintilografia estática; DTPA: cintilografia dinâmica

- **Ultrassonografia:** A primeira ultrassonografia (US) pós-natal foi realizado após a primeira semana de vida, exceto para os casos suspeitos de grave hidronefrose bilateral, quando foi realizado logo após o nascimento. Foram realizados exames ecográficos a cada seis meses até o desaparecimento da dilatação. Se submetidos à intervenção cirúrgica, a avaliação foi realizada em média a cada quatro meses após o procedimento. Os exames foram realizados em equipamento GE (Logiq Book XP), na posição supina. As seguintes mensurações renais foram registradas: comprimento no corte longitudinal, diâmetro transversal e ântero-

posterior dos rins no corte transversal (figura 3). O volume renal foi calculado de acordo com a fórmula proposta por Han & Babcock (2). A pelve renal foi mensurada no corte transversal (DAP e diâmetro transversal). A razão entre o DAP e o diâmetro ântero-posterior do rim foi calculada para todas as unidades (3). A gravidade da hidronefrose foi graduada de acordo com a escala padronizada pela SFU (Society of Fetal Urology) (4). Todas as medidas da pelve renal foram realizadas quando a criança estava com a bexiga vazia (5).

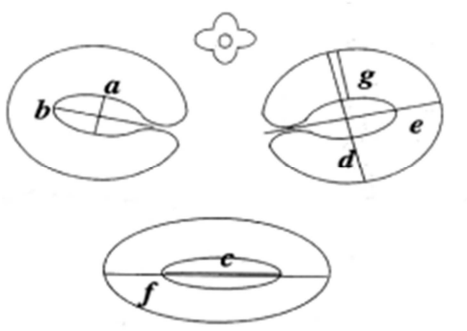

Figura 3 - Dimensões da pelve e das unidades renais mensuradas pela ultrassonografia: (a) diâmetro ântero-posterior da pelve renal; (b) diâmetro transverso da pelve renal; (c) diâmetro longitudinal da pelve renal; (d) diâmetro ântero-posterior do rim; (e) diâmetro transversal do rim; (f) diâmetro longitudinal do rim; (g) espessura do parênquima renal.

- **Uretrocistografia miccional:** A avaliação contrastada do trato urinário baixo foi obtida no primeiro mês de vida, após exclusão de infecção urinária através do exame de urocultura negativa, sempre precedida de cobertura antibiótica profilática com ¼ da dose terapêutica de cefalosporina de primeira geração (cefalexina ou cefadroxila) em dose única diária. Os exames foram realizados no Serviço de Radiologia do HC/UFMG, segundo técnicas e normas padronizadas por radiologistas que desconheciam as dimensões da pelve renal à ultrassonografia (6).

- **Cintilografia renal:** A morfologia do parênquima renal foi estudada utilizando-se radioisótopos: DMSA para quantificar a captação do parênquima renal e DTPA para a avaliação do fluxo e excreção renal. Em caso de dilatação de pelve renal maior 10 mm, foram obtidas cintilografia estática e cintilografia dinâmica após o primeiro mês de vida. Nos casos de RVU, apenas a cintilografia estática foi obtida.

- **Exames laboratoriais:**

- **Dosagem sérica de ureia e creatinina:** Os testes séricos de função renal foram coletados após 72 horas de vida e, em seguida, semestralmente no primeiro ano de vida, após anualmente durante o acompanhamento clínico, ou antes, se o houvesse necessidade clínica. A função glomerular foi estimada de acordo como a fórmula convencional proposta por Schwartz et al até 2011 (7, 8). Após 2011, a creatinina passou a ser mensurada usando o método IDMS. Desde então, a formula adotada para estimar a função renal foi a formula de Schwartz modificada (8).

Quando a suspeita diagnóstica foi de válvula de uretra posterior ou outra condição na qual poderia haver comprometimento da função renal, esses exames foram realizados logo após o nascimento e repetidos em 72 horas.

- **Urina rotina e urocultura:** Amostras de urina de todos os recém-nascidos foram obtidas para urinálise e cultura após o primeiro dia de vida e subsequentemente a cada visita clínica ou quando houve suspeita clínica de ITU. Os exames foram coletados no Laboratório Central do Hospital das Clínicas da UFMG, com técnicas padronizadas. Piúria significativa foi definida como o achado de 5 ou mais leucócitos por campo em microscópio com 400 vezes de aumento. A urocultura foi considerada positiva quando houve isolamento de uma única bactéria, com valor igual ou superior a 100.000 unidades formadoras de colônia (UFC)/ml, na vigência de sintomatologia. A técnica de coleta foi a seguinte: espécimes de urina para cultura foram cuidadosamente coletadas por profissionais treinados do Laboratório Central do HC/UFMG. Para crianças com controle de esfíncter, foi obtida coleta do jato médio em recipiente estéril após higiene da área em torno do meato uretral com água e sabão. Para lactentes, a amostra de urina foi obtida com uso de saco plástico coletor após completa higiene da área perineal. O saco coletor foi trocado a cada 30 minutos para assegurar uma obtenção de amostra adequada, sendo prontamente removido após a micção. A amostra de urina foi imediatamente processada ou colocada em refrigerador apropriado.

Foi diagnosticado ITU quando o paciente apresentava clínica e exames laboratoriais alterados.

- **Conduta cirúrgica:** Para os casos de uropatias obstrutivas, foi tentada uma abordagem não cirúrgica em pacientes com dilatação pélvica leve/moderada, unidades renais com função preservada (40%) e um padrão não obstruído ao

DTPA. Pacientes com dilatação grau IV (SFU), função moderada ou gravemente acometida e curva de padrão obstrutivo ao DTPA foram tratados cirurgicamente de acordo com a uropatia diagnosticada. Os pacientes foram prospectivamente acompanhados e exames de imagem foram realizados aproximadamente seis meses após a cirurgia ou após a avaliação inicial.

4.1.4. ANÁLISE ESTATÍSTICA

As estatísticas descritivas foram apresentadas como mediana e intervalo interquartílico ou frequência. Dados faltantes das variáveis preditivas candidatas foram submetidos à imputação múltipla dos dados. Cada dado faltante foi imputado cinco vezes. Valores imputados foram tirados de uma distribuição preditiva em um modelo de imputação que incluiu todos os preditores candidatos e o desfecho. Os resultados foram combinados para produzir estimativa global e erros padrão que refletissem a incerteza dos dados faltantes (9).

A curva de Kaplan-Meier com logrank foi utilizada para ilustrar as associações das variáveis preditoras estudadas com necessidade de cirurgia em analise univariada. O modelo de risco proporcional de Cox foi usado para calcular a associação entre preditores candidatos com a ocorrência de cirurgia. A taxa de falha e o intervalo de confiança (IC) de 95% foram utilizados para medir associação entre grupos. A taxa de falha para variáveis contínuas foi expressa pelo percentil 75 versus percentil 25. Apenas aquelas variáveis que foram associadas com o evento de interesse na analise univariada ($p<0,25$) foram incluídas no modelo de taxas de falha proporcionais de Cox. Então, utilizando a estratégia estatística de backward, foram incluídas no modelo final aquelas variáveis que permaneceram independentemente associadas com o desfecho. Todos os valores de p foram bi-caudais e o valor de p menor que 0,10 foi considerado estatisticamente significativo.

Um modelo preditivo foi, então, construído a partir desses dados, dividindo cada coeficiente β no modelo multivariado final pelo menor coeficiente β encontrado nessa análise. Assim, utilizando-se esses resultados, foi atribuído um peso para cada variável do modelo. Finalmente, um escore de risco para cada paciente foi obtido pela soma dos pesos para cada variável presente (10). Os escores de risco obtidos para os pacientes foram agrupados e três grupos de risco para necessidade de cirurgia e foram, então, identificados: baixo risco, risco intermediário e alto risco.

Durante o desenvolvimento de modelos de predição, estes apresentam um desempenho otimista e super ajustado. Para corrigir o otimismo e o super ajuste, foi realizada uma validação interna pelo método de reamostragem bootstraping. Cem amostras foram retiradas com substituição. Um modelo de predição foi desenvolvido com cada amostra e o desempenho foi avaliado nas amostras do bootstrap e na amostra original (11, 12). Os coeficientes do modelo final foram corrigidos pela técnica de shrinkage. A discriminação do modelo indica quão bem o modelo de predição é capaz de distinguir entre pacientes que irão vivenciar o desfecho e aqueles que não irão. A discriminação é acessada através da estatística *c*. Sua interpretação é equivalente à área sob a curva, ou seja, uma estatística c igual a 0.5 indica uma discriminação abaixo da chance e uma estatística *c* igual a 1.0 indica uma discriminação perfeita. A calibração do modelo foi demonstrada pelas curvas de Kaplan-Meier para pacientes em divididos em grupos de risco (baixo, médio e alto risco) e através de gráfico de barras comparando a probabilidade predita e o risco observado com 2 anos de seguimento.

O modelo foi apresentado através de um nomograma onde cada variável preditora pode ser julgada com sua importância relativa pelo número de pontos atribuídos.

As análises estatísticas foram realizadas no programa R versão 2.13.1 (*R Foundation for Statistical Computing, Vienna, Austria*) no programa SPSS versão 18.0 (SPSS, Inc., Chicago).

4.1.5. **ASPECTOS ÉTICOS**:

O estudo foi aprovado pelo comitê de ética da UFMG e os pais ou responsáveis legais das crianças assinaram um termo de consentimento livre e esclarecido.

4.2. ESTUDO MODELO DE PREDIÇÃO VUP X DRC

4.2.1. **PACIENTES:**

Todos os pacientes admitidos com o diagnóstico de VUP (n=178) admitidos na Unidade de Nefrologia Pediátrica do Hospital das Clínicas/UFMG de 1970 a 2015.

Foram registrados, em protocolo próprio, os dados clínicos, os exames laboratoriais e de imagem à admissão e durante toda a evolução, o tratamento e os dados evolutivos de cada paciente. Para o presente estudo, foi desenvolvido um banco de

dados específico no programa Statistical Package for the Social Sciences (SPSS) versão 18.0.

- **Critérios de inclusão:** Crianças portadoras de VUP acompanhadas na Unidade de Nefrologia Pediátrica de 1970 a 2015.

- **Critérios de exclusão:** Pacientes que interromperam o acompanhamento logo após o nascimento (n= 5).

4.2.2. **DELINEAMENTO:**

O delineamento da pesquisa é de um estudo de coorte retrospectivo, sendo os dados coletados de pacientes acompanhados entre 1970 e 2015. Com a finalidade de atender os objetivos propostos foi feita a identificação de fatores de risco potenciais que foram independentemente associados à evolução para DRC estágio ≥ 3 e estágio 5 durante o período de seguimento e determinação de um modelo de predição de evolução para DRC ≥3.

- **Desfecho clínico de interesse:** o desfecho clínico de interesse evolução para DRC estágio ≥ 3 e estágio 5. DRC foi classificada de acordo com os estágios propostos pela the National Kidney Foundation practice guidelines (13). DRC estágio 5 foi definida como ritmo de filtração glolmerular menor que 15 mL/min em 3 exames consecutivos e/ou a necessidade de terapia de substituição renal crônica.

- **Variáveis explicativas:** As seguintes variáveis foram incluídas na análise: período de admissão (1970-1989 versus 1990-2015), apresentação clínica (pré-natal e pós-natal), presença de RVU, lateralidade do RVU (unilateral vs bilateral), creatinina à admissão, ritmo de filtração glomerular à admissão, nadir de creatinina (menor valor da creatinina durante o primeiro ano após intervenção cirúrgica), episódios de infecção do trato urinário, intervenção cirúrgica primária. Duas variáveis tempo-dependente foram incluídas na análise: proteinúria e hipertensão.

4.2.3. PROTOCOLO CLÍNICO

- **Pacientes com diagnóstico pré-natal: condução semelhante ao item 1.1.3.**

- **Pacientes com diagnóstico pós-natal:** a maioria dos pacientes foi diagnosticada no contexto de investigação de um episódio ou episódios recorrentes de ITU.

- **Acompanhamento clínico:** após avaliação inicial e intervenção cirúrgica, consulta clínica, exames de laboratoriais (uréia, creatinina, urina rotina, urocultura, proteinúria amostra única e/ou 24h) e de imagem foram realizados a cada seis meses, ou antes, se necessário. A consulta clínica consistiu de exame físico, incluindo medidas antropométricas e de pressão arterial. Culturas de urina foram obtidas em cada consulta ou após qualquer episódio de febre sem foco definido ou na presença de sintomas urinários. Cultura de urina foi coletada de maneira apropriada no laboratório do HC/UFMG.

A creatinina plasmática foi colhida na admissão e semestralmente, ou antes, se necessário. A função glomerular foi estimada de acordo como a fórmula convencional proposta por Schwartz et al até 2011 (7, 8). Após 2011, a creatinina passou a ser mensurada usando o método IDMS. Desde então, a formula adotada para estimar a função renal foi a formula de Schwartz modificada (8).

ITU foi definida como o crescimento de pelo menos 100.000 ufc/mL de urina de um uropatógeno obtida por saco coletor ou jato médio com febre (38 °C ou mais) e/ou sintomas urinários.

Após o tratamento do primeiro episódio de ITU e irradicação da infecção com negativação da urocultura, foi iniciada a profilaxia com antibiótico. Utilizou-se a cefalosporina de primeira geração (cefalexina 50mg/dia) nos dois primeiros meses de vida. Após essa faixa etária, a profilaxia foi modificada para sulfametoxazol+trimetoprim (1-2mg/kg/dia de trimetoprim) ou nitrofurantoína (1-2mg/kg/dia) em dose única diária. A profilaxia foi mantida enquanto aguardava-se propedêutica de imagem, até a correção cirúrgica e para pacientes com refluxo vesicoureteral (RVU) maior ou igual a três até os 6-7 anos de idade.

A medida da pressão arterial sistêmica foi realizada em todas as consultas médicas, com a utilização de esfigomomanômetro de tamanho apropriado para a idade, como recomendado pelo *Working Group of the National High Blood Pressure Education Program* (1). Foram considerados os valores de referência e definições empregadas no estudo da *Fourth Task Force on Blood Pressure in Children (1).* Para

pacientes acima de 17 anos de idade, foi considerado hipertensão, valores consistentemente acima de 140/90 mm Hg.

A presença de proteinúria foi considerada quando a razão proteína/creatinina estava acima de 0.2 ou proteinúria de 24 horas acima de 150 mg/dia em pelo menos duas avaliações consecutivas.

- **Investigação por imagem:** A investigação do trato urinário foi obtida de acordo com algoritmo abaixo (figura 4):

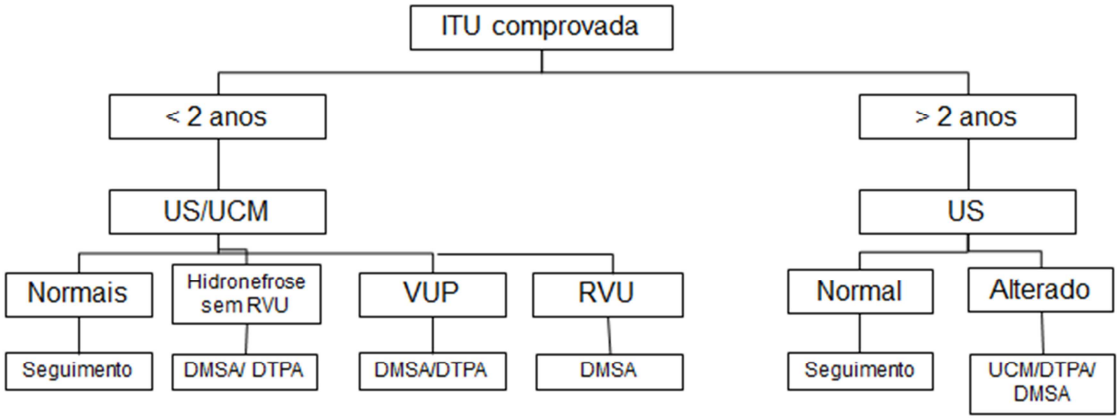

Figura 4: Algoritmo para avaliação do trato urinário em crianças com ITU comprovada

US: ultrassonografia; UCM: uretrocistografia miccional; RVU: refluxo vesicoureteral; VUP: válvula de uretra posterior; DMSA: cintilografia estática; DTPA: cintilografia dinâmica

4.2.4. ANALISE ESTATISTICA

Os valores foram expressos como mediana e intervalo interquartílico, frequência ou media e desvio padrão, quando apropriado. Possíveis covariáveis preditivas dos desfechos foram avaliadas pelo modelo de Cox convencional e pelo modelo de Cox com variável tempo-dependente. No modelo com variáveis fixas, apenas as covariáveis presentes até o primeiro ano de vida foram incluídas. Assim, por exemplo, apenas pacientes que apresentaram hipertensão e ou proteinúria até 12 meses foram considerados na análise. O modelo com variáveis tempo-fixas foi conduzido em duas etapas. Na primeira etapa, a análise univariada foi realizada para identificar variáveis que foram significantemente associadas com o desfecho. A análise de sobrevida foi

realizada pelo método de Kaplan-Meier para avaliar o tempo ate a ocorrência dos desfechos estudados: DRC ≥ 3 ou DRC estagio 5. Hazard ratio ou razão de taxa de falha (HR) e o respectivo IC a 95% foram usados na analise univariada (regressão de Cox). As diferenças entre os subgrupos foram avaliadas pelo teste de log-rank bicaudal. O modelo de taxas de falha proporcionais de Cox foi utilizado para identificar as variáveis que foram independentemente associadas à ocorrência de DRC ≥ 3 ou DRC estagio 5. Apenas aquelas variáveis que foram associadas com o evento de interesse na analise univariada ($p<0,25$) foram incluídas no modelo de Cox. Então, utilizando a estratégia de *backward elimination*, foram incluídas no modelo final aquelas variáveis que permaneceram independentemente associadas com o desfecho. Todos os valores de p foram bicaudais e o valor de $p<0,05$ foi considerado estatisticamente significativo.

Um modelo preditivo foi, então, construído a partir desses dados, dividindo cada coeficiente β no modelo multivariado final pelo menor coeficiente β encontrado nessa analise. Assim, utilizando-se esses resultados, foi atribuído um peso para cada variável do modelo. Finalmente, um escore de risco para cada variável presente foi obtido pela soma dos pesos para cada variável presente (10). Os escores de risco obtidos para os pacientes foram agrupados e três grupos de risco para DRC≥ 3 foram, então, identificados: baixo risco, risco intermediário e alto risco.

Durante o desenvolvimento de modelos de predição, estes apresentam um desempenho otimista e super ajustado. Para corrigir o otimismo e o super ajuste, foi realizada uma validação interna pelo método de reamostragem bootstraping. Cem amostras foram retiradas com substituição. Um modelo de predição foi desenvolvido com cada amostra e o desempenho foi avaliado nas amostras do bootstrap e na amostra original (11, 12). Os coeficientes do modelo final foram corrigidos pela técnica de shrinkage.

A discriminação foi avaliada usando a estatística *c*, que representa a área sobre a curva ROC (receiver operating characteristic curve). A maior área indica a melhor discriminação. A avaliação da calibração do modelo (o quanto mais próximo as probabilidades preditivas refletem o risco atual) para a predição de DRC≥ 3 foi determinado na população estudada pelo método de Kaplan-Meier. Por fim, foi estimada pelo método de Kaplan-Meier a probabilidade de sobrevida renal de acordo com as categorias de risco (baixo risco, risco intermediário).

4.2.5. **ASPECTOS ÉTICOS**:

O estudo foi aprovado pelo comitê de ética da UFMG e os pais ou responsáveis legais das crianças assinaram um termo de consentimento livre e esclarecido.

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5. RESULTADOS E DISCUSSÃO

5.1. ARTIGO ORIGINAL I

Development of a Prognostic Model for need of surgical intervention in Children with Congenital Anomalies of the Kidney and Urinary Tract

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Key words: congenital anomalies of kidney and urinary tract, surgery, prognostic model

Abstract

Purpose: To develop a prognostic model for the need of surgery in patients with congenital anomalies of kidney and urinary tract (CAKUT).

Patients and Methods: This is a cohort study of 694 children with CAKUT admitted at the pediatric nephrology unit of our institution. Children were included between 1987 and 2013. The median age at admission was 2 months and 65% were male. Considered patient characteristics at baseline were: gender, age, serum creatinine, estimated glomerular filtration rate (eGFR), oligohydramnios, presence of other urinary tract anomalies associated with renal pelvic dilatation (RPD) (megaureter, megacystis), anteroposterior renal pelvic dilatation (APRPD) laterality (unilateral vs bilateral), presence of renal lesions (RL) on Tc-99m DMSA scan, APRPD magnitude and period of admission (before vs after 2000). A prognostic model was developed using Cox proportional hazard regression analysis and backward selection. Internal validity was studied in 100 bootstrap samples.

Results: A total of 164 (23%) patients were submitted to surgery at a median age of 7.8 months. The predictors included in the model were eGFR, presence of other urinary tract anomalies associated with RPD, presence of RL on Tc-99m DMSA scan, APRPD magnitude and period of admission. The optimism corrected c statistic was 0.84.

Conclusions: Our prognostic model for the need of surgery may contribute to identify CAKUT patients at high risk for surgical intervention. Further studies are necessary to validate the model in independent samples of CAKUT patients.

INTRODUCTION

Congenital anomalies of kidney and urinary tract (CAKUT) are among the most common fetal malformations with an incidence of 1-14 cases per 1000 births (1, 2). CAKUT comprises a wide phenotypic spectrum and the most commonly involved anomalies are non-obstructive hydronephrosis, ureteropelvic junction obstruction, vesicoureteral reflux, ureteropelvic junction obstruction, posterior urethral valve, primary megaureter and multicystic dysplastic kidney (3). CAKUT are important causes of kidney morbidity and the most frequent cause of chronic kidney disease (CKD) and end-stage renal disease in infants and young children (4, 5).

In spite of the continuous advances in the understanding of the genetic basis and outcomes of CAKUT, there are still many controversies regarding the clinical significance, postnatal evaluation, and management of infants. Consequently, taken into account the heterogeneity of CAKUT, there is an understandable little consensus about the best approach for these patients (6-10). The management of these anomalies is a challenge for the medical team including neonatologists, pediatricians, pediatric nephrologists and pediatric urologists. In this setting, a relevant issue concerning the management of CAKUT is to establish a consistent approach to discern which patients would benefit from surgical intervention and which may be best assisted by continued surveillance. (7, 11-13). Nevertheless, there has been scarce literature concerning predictive models of the need of surgical intervention in this population (14). Retrospective cohort studies have suggested some variables as prognostic factors for surgery or for spontaneous resolution of renal pelvic dilatation (15-18). Prognostic factors that have been reported include anteroposterior of renal pelvic diameter (APRPD), renal cortical thickness, differential renal function on renal scintigraphy (11, 12, 16, 18-21). We have previously described the clinical course of children with prenatally detected CAKUT and we identified variables that are possible predictors of progression to CKD (22). The aim of this retrospective cohort study was to identify potential prognostic factors for the need of surgery in a large series of patients with CAKUT. In addition, we combined the strongest factors in a model to assess individualized risk of surgery need. Such a model may identify patients at high risk for surgical management.

Patients and methods

Patients. All infants with diagnosis of CAKUT (n=819) admitted at the Pediatric Nephrology Unit (Hospital das Clínicas, Federal University of Minas Gerais (UFMG), Brazil) from 1987 to 2013 were followed-up. Patients with aneuploidy, multiple malformations, neurogenic bladder or loss of follow-up soon after the birth were excluded (n = 125). In total, 694 infants were included in the analysis.

Clinical protocol. During the 25 years of this study, the clinical protocol for the management of infants with perinatal diagnosis of CAKUT has inevitably evolved. In the first decade of the study, infants were investigated according to a comprehensive systematic protocol described elsewhere (23). Briefly, all patients with anterior posterior renal pelvis dilatation (APRPD) equal or greater than 5 mm were placed on prophylactic antibiotics at birth and submitted to an extensive imaging workup, including renal ultrasonography (RUS), voiding cystourethrogram (VCUG), and renal scintigraphy. After 2000, we developed a more tailored clinical protocol, based mainly on the severity of the renal pelvic dilatation (21). Briefly, all infants were submitted to VCUG within three months of life. Regarding imaging workup, a US scan was performed after the first week of postnatal life, and, until 2009, all infants underwent a voiding VCUG. Since 2009, VCUG has been indicated for a selected subgroup of patients with fetal or postnatal APRPD > 10 mm and or ureter dilatation. Renal scintigraphy (Tc-99m DMSA and Tc-99m DTPA) was performed after the first month of life in patients with APRPD equal or greater than 10 mm. Antibiotic prophylaxis was started on the first postnatal day and maintained in accordance with the postnatal diagnosis.

Follow-up protocol. After initial clinical and imaging evaluation, RUS scans, clinical visits, and laboratory reviews (including urine culture and serum creatinine) were scheduled at 6-month intervals. In short, the clinical approach consisted of full physical examination, including evaluation of anthropometric measurements and blood pressure performed at 6-month intervals. Urine cultures were obtained on each 6-month follow-up visit, and it was recommended that urine samples be collected during any unexplained febrile episode or in the presence of urinary symptoms (24).

Outcome: Prognosis was defined as the time from birth until the first surgical intervention.

Candidate predictors. The following variables at baseline were considered in the analysis: gender, age, serum creatinine, estimated glomerular filtration rate (eGFR), oligohydramnios, presence of other urinary tract anomalies associated with renal pelvic dilatation (RPD: megaureter, megacystis), APRPD laterality (unilateral vs bilateral), presence of renal lesions (RL) on Tc-99m DMSA scan, APRPD magnitude and period of admission (before or after 2000). Combined data obtained by VCUG, renal scan and sequential RUS were considered for the diagnosis of urinary tract anomalies. The absence of any recognized uropathy was classified as idiopathic hydronephrosis. Isolated hydronephrosis was defined as the presence of APRPD $\geq$ 5 mm without any other alterations of the urinary tract. Associated hydronephrosis was defined as the presence of APRPD >5 mm combined with other alterations, such as megaureter and megacystis. When bilateral renal pelvic dilation was present, the largest APRPD was considered for analysis. Tc-99m DMSA RL was classified as none, unilateral and bilateral when there was renal scarring in none, one or both kidneys, respectively. Oligohydramnios was determined on the basis of the amniotic fluid index (25). Since creatinine measurements were made using the Jaffe method until November 2011 in our institution, glomerular filtration rate (eGFR) was estimated by the conventional Schwartz formula (26) for data obtained until this period. After November 2011, creatinine was measured using the IDMS traceable method. Therefore, the modified Schwartz formula (27) was adopted to estimate eGFR rather than the conventional Schwartz formula.

Statistical analysis and development of the risk prediction model. Missing values for candidate predictors were multiple imputed (MI). Each missing value was imputed five times. Imputed values were drawn from the predictive distribution in an imputation model that included all candidate predictors and the prognosis. MI resulted in five complete datasets, which were analyzed with standard complete data methods. The results were combined to produce overall estimates and standard errors that reflect missing data uncertainty (28, 29). Cox proportional hazards regression analysis was used to assess the association between the candidate predictors and the occurrence of surgery. Hazard ratios for continuous variables were given for the 75 percentile versus 25 percentile of the variable. Using a backward elimination strategy with $p < 0.1$, the strongest prognostic factors were included in the final model (30).

When prediction models are developed in relatively small samples, they may be overfitted and may show optimistic performance. To adjust for overfitting and optimistic performance of the model, we used bootstrap resampling for internal validation. One hundred bootstrap samples were drawn with replacement; a prognostic model was developed in each sample; and the performance was evaluated in the bootstrap sample and in the original sample. The average calibration slope of the bootstrap procedure was used to shrink the regression coefficients in the final model.

The model was presented as a nomogram where each predictor could be judged its relative importance by the number of points attributed over the range of the predictor (31, 32).

Statistical analyses were performed with R software version 2.13.1 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS version 18.0 (SPSS, Inc., Chicago).

Ethical aspects. The study was approved by the Ethics Committee of the UFMG and the parents or legal guardians responsible for the children gave written informed consent to participate.

RESULTS

A total of 164 (24%) patients underwent surgery at a median age of 7.8 months (interquartile range (IQR), 2.4-16.1 months). The majority of patients were boys, considering the entire CAKUT group (65%) as well the subgroup of children submitted to surgical intervention (76%). The median follow-up for patients who did not undergo surgical intervention was 50 months (IQR, 25-154 months).

Table 1 shows the baseline characteristics and association between patient characteristics and the need of surgery.

Table 1

Age, oligohydramnios, serum creatinine, eGFR, associated urinary tract anomalies with RPD, APRPD laterality, presence of RL on Tc-99m DMSA scan, APRPD magnitude and period of admission showed an association with the need of surgical intervention (Figure 1).

Figure 1

After backward selection, five predictors remained in the model: eGFR, associated urinary tract anomalies with RPD, presence of RL on Tc-99m DMSA, APRPD magnitude and period of admission (Table 2).

Table 2

The uniform shrinkage factor estimated with bootstrapping was 0.94. The *c* statistic was 0.84 (IC95% 0.82-0.87) after correction for optimism.

The prediction model is presented as nomogram and provides the risk that a patient needs surgery within 2 years (Figure 2). To use the nomogram, a line from each predictor value needs to be draw upwards to the point axis. Then, the points corresponding to the predictor values need to be added and the result be located to the Total Points axis. A line from the total points value to the axis for 2 years risk of surgery need to be drawn to find the patient`s risk of surgery within 2 years of follow-up.

For example, a child with eGRF of 40 ml/min/1.73 m^2 (7 points), associated urinary tract anomalies with RDP (5 points), bilateral RL on Tc-99m DMSA scan (9 points), APRPD magnitude of 40 mm (10 points), time of diagnosis after 2000 (0 points). The total points of 31 correspond to a risk of undergoing surgery before the age of 2 of 90%.

The formula with shrunk coefficients to calculate the individual absolute risks of needing surgery is described in figure 3. We divided the risk score into tertiles: low-risk (<20 points), medium-risk (20-28 points) and high-risk (29+ points). High-risk patients showed a 2 year risk of needing surgery of 55% (Figure 4). Figure 5 shows the calibration plots (predicted vs observed) for the model of risk prediction during 2 years of follow-up.

Figure 2

Figure 3

Figure 3

Figure 4

DISCUSSION

In this study, we evaluated prognostic factors for the need of surgical intervention in a large cohort of children with CAKUT, who were included between 1987 and 2013. About a quarter of these patients needed surgical intervention; children born after 2000 needed less often surgery (15%). The strongest prognostic factors for the need of surgery were eGFR, associated urinary tract anomalies with RPD, presence of RL on Tc-99m DMSA and the APRPD magnitude. We combined the factors in a prognostic model that showed good predictive performance.

CAKUT is a heterogeneous and complex group of diseases associated with UTI, CKD and hypertension in children. These anomalies are the most common cause of CKD in childhood (4). The majority of CAKUT is non-surgically managed, but, in some cases, surgery will be necessary. Nevertheless, controversies still exist about which children and when submitting to surgery (2, 17, 33, 34). Unnecessary interventions should be avoided, but late procedures could enhance the risk of infection and renal parenchymal loss (34). During the follow up the medical team requests imaging workup and laboratory tests to assess the diagnosis of uropathy and to choose the best management (9). So far, a reference test is not available to define which patient at what time will need surgery. Early identification of patients at high risk for needing surgical procedures may be helpful for medical decisions and may decrease unnecessary interventions in low risk patients.

We found that before the year 2000, the surgical management was more common than after 2000. This finding is consistent with the current literature that recommends nonsurgical treatment for the majority of patients with CAKUT. (2, 6-10, 19, 35-38).

Some studies have identified possible prognostic factors for the need of surgery in patients with CAKUT (16, 20, 39, 40). For instance, Nef et al. reported impaired renal function, oligohydramnios and postnatal bilateral renal anomalies as prognostic factors (39). The latter two were also associated with need of surgery in the current cohort, but not selected in the model. Possibly, the statistical power to identify oligohydramnios as important prognostic factor was too low, because of the high rate of missing data in our database concerning the amniotic fluid.

The magnitude of renal pelvis dilatation is the most commonly found prognostic factor for need of surgery. Most studies use the measurement of antenatal APRPD (16, 19, 20, 40). Some used antenatal hydronephosis (ANH) and found a major incidence of surgery in patients with higher risk for higher SFU 3 and 4 (19). Similarly, Plevani et al analyzed patients with ANH. The need for postnatal surgery increased significantly with the degree of renal pelvis dilatation: 0%, 10.1% and 33.3% for ANH of first, second and third degree, respectively. Compared non-surgical cases, the surgical cases had greater in utero AP diameter (10.2 ± 4.3 vs. 17.1 ± 11.0 mm, $P < 0.001$) and a higher rate of associated urinary tract anomalies (6.7 vs. 88.9%, $P < 0.001$) (16). In our study, associated RPD was strongly associated to need of surgery. Similarly, Plevani et al in their study found that the presence of associated urinary tract anomalies and magnitude was independent predictors of postnatal surgery (16).

Some authors recommended surgery in patients with differential renal function (DRF) less than 40% (12, 34, 41). We have categorized the presence of renal lesions as none, unilateral and bilateral, since patients with bilateral renal lesions could have normal DRF. Unilateral and bilateral renal lesions on DMSA were predictors for surgery in our cohort.

Clinical and methodological issues should be taken into account in evaluating our findings. From the methodological point of view, we did not have validated our prognostic model in an independent cohort. External validation is important, because accurate predictions in the development cohort, do not necessarily guarantee good predictions in other patients (30, 42, 43). A clinical weakness is that the medical team decided who needed surgery. The end-point is hence subjective and probably based on the variables in the model. That would imply that we modelled the decision making of the surgery rather than need of surgery. However, the children who did not undergo surgery, most likely did not need surgery, given the long follow-up time. False positives, i.e. children who underwent surgery, but did not need it, could not be identified. Our population contains a variety of phenotypes of CAKUT, with a mixing of isolated hydronephrosis and more complex entities, which may disturb accurate predictions. Including a factor that indicates the phenotype of CAKUT did not improve the model performance. On the other hand, some features of our study may increase the strength of our findings, including the large dataset collected over many years, the

length of the follow-up time, and the management by the same medical team using an standardized protocol.

In summary, we have developed a clinical prognostic model for need of surgical intervention in children with CAKUT. The magnitude of renal pelvic dilatation, renal function at baseline, presence of associated urinary tract anomalies with RPD, and presence of renal lesion remained as predictors of surgical intervention. We believe that this prognostic model, after external validation, can support the medical team to identify infants with CAKUT at high-risk for surgical intervention in the first years of life.

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TABLES:

Table 1 - Patient characteristics and association with the need for surgery, Pediatric Nephrology Unit, HC/UFMG, 1987-2013.

		Surgery		
Characteristics	**Unit or category**	**Yes** N = 164	**No** N = 530	**Hazard Ratio [95%CI]**
Gender	male	124 (76%)	329 (62%)	1.2 [0.82 – 1.6]
Age at admission	months	1.1 (0.19 - 2.9)	2.2 (0.82 - 4.9)	1.1 [1.0 – 1.2]*
Plasma Creatinine	mg/dl	0.50 (0.39 - 0.73)	0.36 (0.30 - 0.50)	1.2 [1.1 – 1.2]
eGRF	ml/min/1.73m²	52 (31 - 75)	71 (51 - 92)	2.2 [1.7 - 2.9]*
Oligohydramnios	yes	14 (8.5%)	12 (2.3%)	3.7 [2.1 – 6.4]
missing	426			
Associated RPD	yes	92 (61%)	160 (31%)	3.0 [2.2 - 4.2]
missing	25			
Bilaterality	yes	63 (45%)	220 (43%)	1.2 [0.83 - 1.6]
99mTC –	none	55 (38%)	200 (69%)	reference
DMSA lesion	unilateral	75 (52%)	84 (28%)	2.6 [1.9 - 3.7]
	bilateral	13 (10%)	9 (3%)	4.3 [2.3 - 7.8]
missing	258			
APRPD	mm	20 (13 - 29)	8 (6 - 12)	1.5 [1.4 - 1.7]
missing	85			
Period of admission	before 2000	80 (49%)	84 (16%)	3.8 [2.7-5.1]

Values are given as number (percentage of observed total) or median (25 – 75 percentile), unless stated otherwise.

Hazard ratios for continuous variables are given for the 75 percentile versus the 25 percentile.

*risk is higher for lower predictor values
eGRF: estimated glomerular renal function; APRPD: anteroposterior renal pelvis dilatation; RPD: renal pelvic dilatation; 95%CI: 95% confidence interval

Table 2 – Multivariable association of the selected prognostic factors with need for surgery, Pediatric Nephrology Unit, HC/UFMG, 1987-2013

Prognostic factor	Unit or category	Harzard ratio [95% CI]
eGFR	47 vs. 90 ml/min/1.73 m²	1.6 (1.3 - 2.0)
Associated RPD	yes	2.3 (1.6 - 3.3)
Tc-99m DMSA lesion	unilateral	2.0 (1.3 – 3.1)
	bilateral	4.3 (2.2 – 8.2)
APRPD	16 vs. 7 mm	1.5 (1.3 - 1.7)
Period of admission	Before 2000	4.2 (2.8 - 6.3)

Hazard ratios for continuous variables are given for the 75 percentile versus the 25 percentile.
eGRF: estimated glomerular filtration rate; APRPD: anterior posterior renal pelvis diameter; RPD: renal pelvic dilatation; 95%CI: 95% confidence interval

FIGURES:

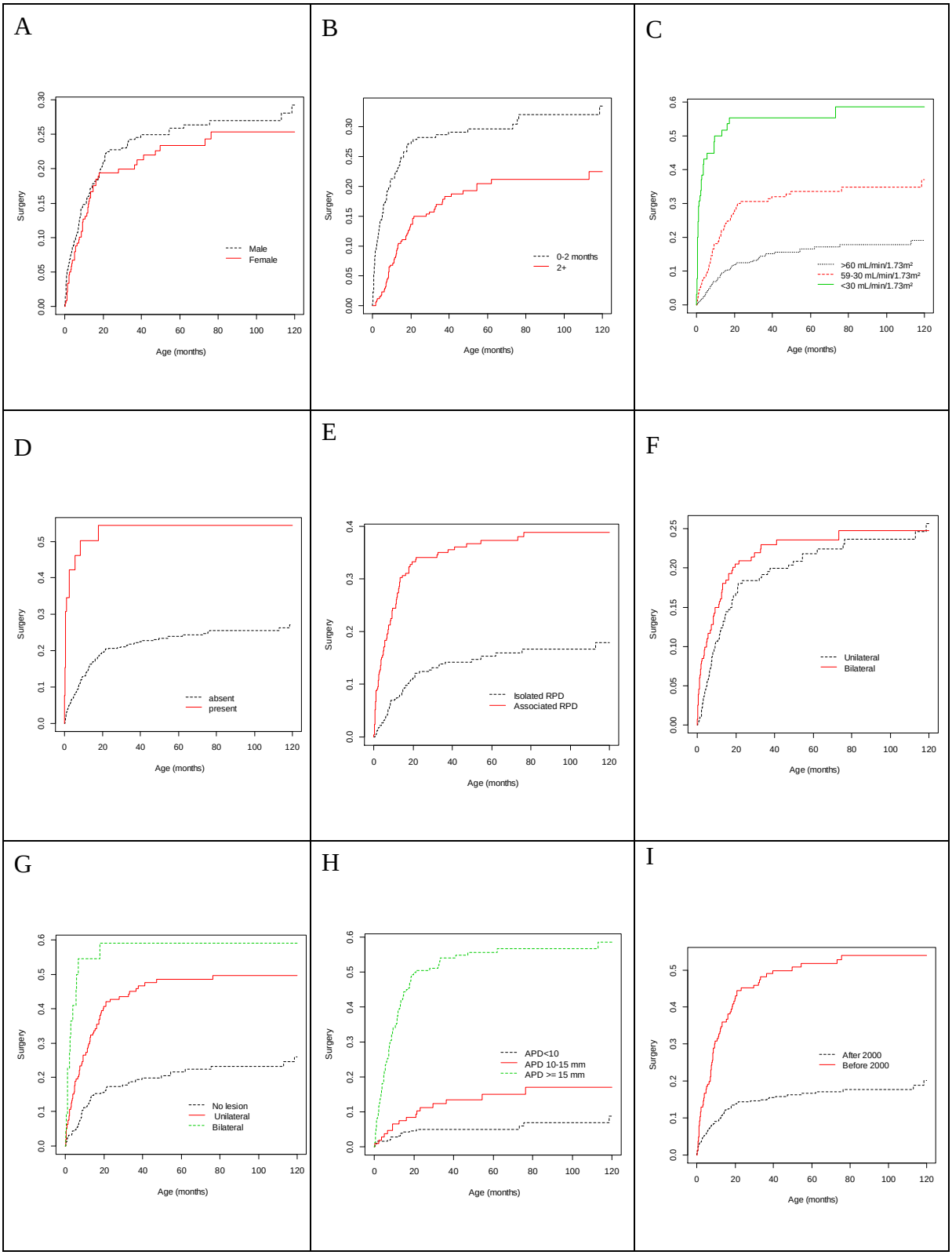

Figure 1: Kaplan Meier estimates for the risk of surgery stratified by gender (A); age in months (B); eGFR (ml/min/1.73 m^2) (C); oligohydramnios (D); associated RPD (renal pelvic dilatation) (E); bilaterality (F); DMSA lesion (G); APRPD magnitude (Anteroposterior diameter /APD in mm) (H); Period of admission (I), Pediatric Nephrology Unit, HC/UFMG, 1987-2013

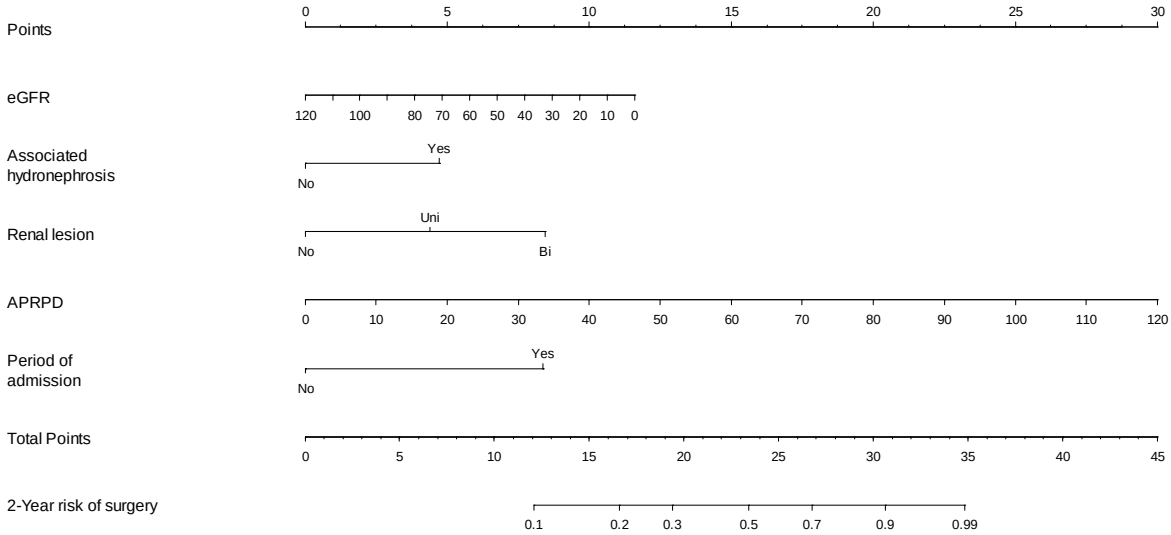

Figure 2: Nomogram for predicting two years risk of surgery based on 5 predictors; Estimated glomerular renal function in mL/min/1.73m^2 (eGFR), Associated hydronefrosis, Presence of renal lesion on DMSA, APRPD (anteroposterior renal pelvis diameter) in mm, period of admission (before 2000) ; 2-year Risk of surgery %, Pediatric Nephrology Unit, HC/UFMG, 1987-2013.

The predicted risk of getting surgery at age *t* in months can be calculated as:

risk (t) = $[1 - S_0(t)^{\exp(lp)}] \times 100\%$, where

$lp = -0.010 \times \text{GFR} + 0.766 \times \text{associated RDP} + 0.625 \times \text{lesion uni} + 1.248 \times \text{lesion bi} + 0.037 \times \text{APRPD} + 1.373 \times \text{diagnosed before 2000}$

$S_0(12) = 0.962$; $S_0(36) = 0.920$; $S_0(60) = 0.910$

with eGFR: estimated glomerular renal function in mL/min/1.73m^2; associated RPD: associated

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Figure 3: Formula with shrunk coefficients to calculate the individual absolute risks of getting surgery: with eGFR: estimated glomerular renal function in mL/min/1.73m^2; associated RPD: associated renal pelvic dilatation(yes=1/no=0); lesion uni: unilateral lesion (yes=1/no=0); lesion bi: bilateral lesion (yes=1/no=0); APRPD: anteroposterior renal pelvis dilatation in mm; diagnosed before 2000 (yes/no)

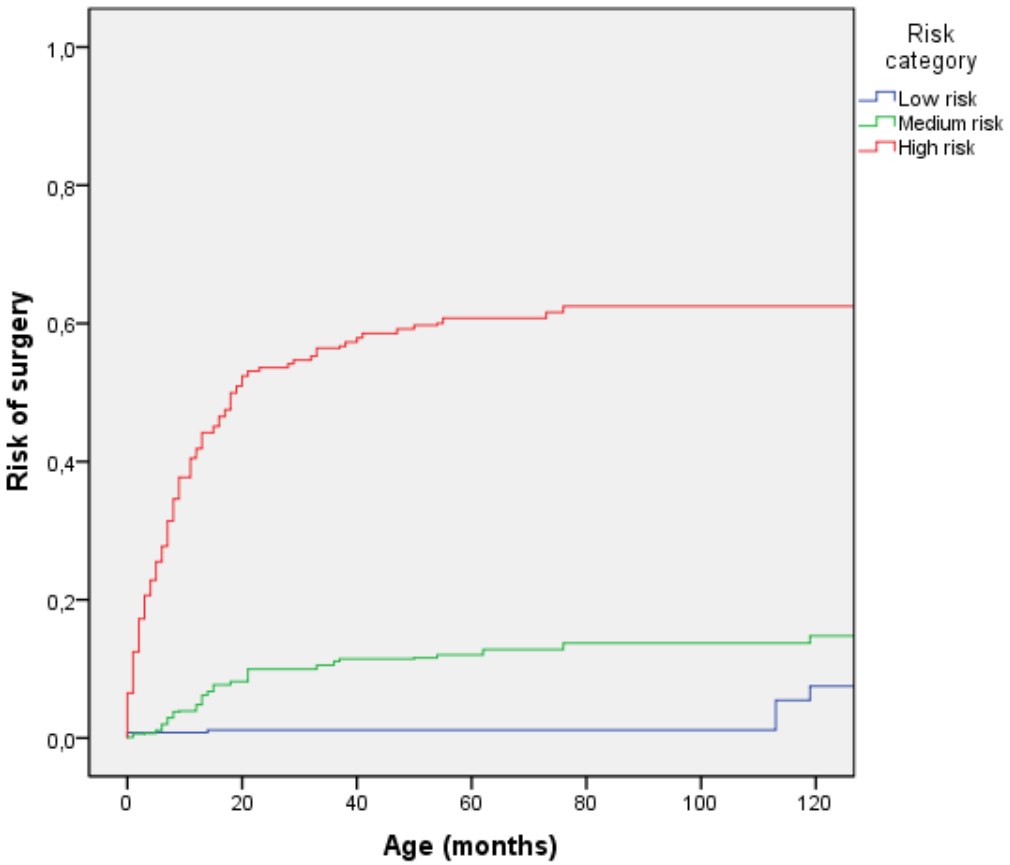

Figure 4 – KM plot for risk of surgery of CAKUT patients by risk category, Pediatric Nephrology Unit, HC/UFMG, 1987-2013

Low-risk category: < 20 points; Medium-risk category: 20-28 points; High-risk category: 29+ points

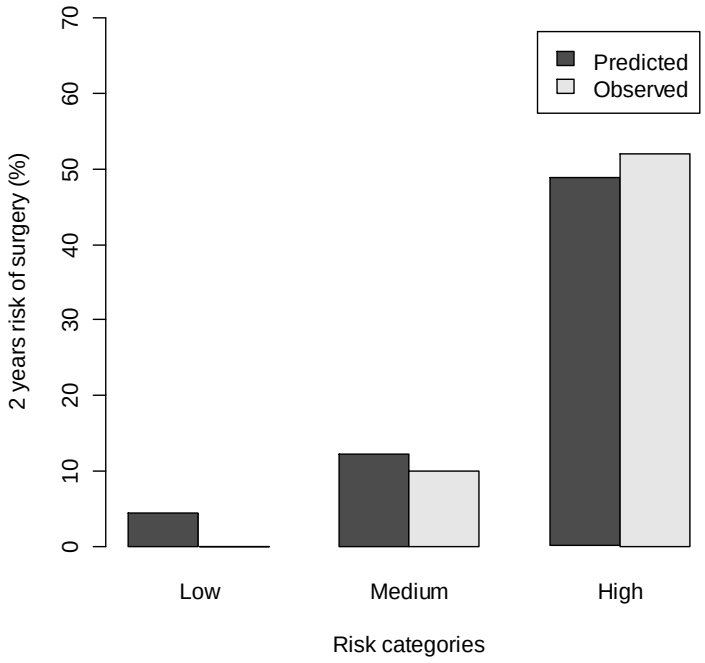

Figure 5 - Agreement between predicted 2 year risk of surgery of patients with CAKUT and observed risk, Pediatric Nephrology Unit, HC/UFMG, 1987-2013.

5.2. ARTIGO ORIGINAL II

Risk factors for chronic kidney disease in children with posterior urethral valves: a time-dependent analysis

Running title: Outcome of posterior urethral valves

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ABSTRACT

Background and objectives: Posterior urethral valves (PUV) constitute the most common infravesical urinary obstruction in boys and are often accompanied by severe consequences to the lower and upper urinary tract. PUV are one of the most common causes of chronic kidney disease (CKD) and end stage renal disease (ESRD) during childhood. The aim of this study was to describe the clinical course and risk factors for CKD in a large cohort of patients with PUV.

Design, setting, participants, & measurements: In this retrospective cohort study, 173 patients with PUV were systematically followed up at a tertiary Pediatric Nephrology Unit. The primary end-points of the study were CKD stage 3 or higher and ESRD. Survival analyses were performed respectively by Cox regression proportional hazard model with time-dependent covariables.

Results: After a mean time of 83 months, 65 children (37.6%) developed CKD stage ≥ 3 and 39 (22.5%) reached CKD stage 5. Fourteen (8.1%) died during follow-up. Thirty-six patients (20.8%) presented hypertension and 78 (45%) exhibited proteinuria during follow-up. After adjustment by the time-dependent Cox model, baseline creatinine, nadir creatinine, hypertension, and proteinuria remained as independent predictors of CKD ≥ stage 3 and ESRD.

Conclusion: Our findings suggest that an earlier identification of risk factors amenable to clinical intervention might contribute to slow the progression of renal impairment.

Keywords: posterior urethral valves - fetal hydronephrosis - vesicoureteral reflux - urinary tract infection – chronic kidney disease – hypertension

INTRODUCTION

Posterior urethral valves (PUV) are the commonest cause of bladder outflow obstruction in male infants. Although not precisely known, its prevalence has been reported as ranging from 1/8000 to 1/25000 live births (1,2). The incidence of PUV has remained steady over the years; however, the presentation and timing of diagnosis has substantially changed (3,4). Currently, most patients have been identified by prenatal sonography due to the presence of hydroureteronephrosis, occasionally associated with megacystis and oligoidramnios (5,6). PUV are often accompanied by severe

consequences to the lower and upper urinary tract (7,8) and are one of the most common causes of chronic kidney disease (CKD) and end-stage renal disease (ESRD) during childhood (9). The morbidity of PUV is related to the congenital obstruction of the urinary tract at a critical time for organogenesis, which may have a profound and lifelong impact on kidney, ureter, and bladder function (10,11).

Over the past two decades, there has been a continuous advance in the understanding of pathophysiology, diagnosis, management and clinical course of PUV (12-15). However, in spite of continuous advances, approximately a quarter of the patients evolved to ESRD during a long-term follow-up (16). Studies that systematically analysed the clinical outcome of patients with PUV are scarce. In addition, the identification of predictive factors for renal impairment may probably contribute to the formulation of therapeutic strategies.

The aim of this study was to evaluate the outcomes of PUV patients treated at tertiary centre between 1970 and 2015, with emphasis on risk factors for the progression to CKD and to ESRD.

PATIENTS AND METHODS

Patients. In this retrospective cohort study, the records of 178 patients with PUVs who were admitted consecutively at the Pediatric Nephrourology Unit of Hospital das Clínicas from Federal University of Minas Gerais (UFMG, Brazil) between 1970 and 2015 were reviewed. We excluded five patients from the analysis due to lost to follow-up.

Baseline data. All patients were admitted to our outpatient facility. For the antenatal cohort, after the initial renal and bladder US (RBUS), neonates with antenatal hydronephrosis suspect of PUV underwent urinary tract imaging workup according to a systematic protocol described in detail elsewhere (17,18). Antibiotic prophylaxis was started at the first postnatal day and was maintained until surgical intervention. For the postnatal cohort, the majority of the cases were diagnosed in the context of the investigation of an episode or recurrent episodes of febrile UTI, as described in detail elsewhere (19,20). Independent radiologists evaluated the association of PUV with vesicoureteral reflux (VUR) based on the findings of conventional voiding cystourethrography.

Follow-up protocol. After initial evaluation and surgical intervention, clinical, laboratory and imaging assessments were carried out periodically at 6-month intervals. Briefly, the clinical approach consisted of full physical examination, including evaluation of anthropometric measurements and blood pressure performed at 6-month intervals or more frequently, whether clinically needed (18,21,22). Urine cultures were obtained at each follow-up visit, and it was recommended that urine samples should be collected during any unexplained febrile episode or in the presence of urinary symptoms. Urine specimens for culture were carefully collected at our hospital outpatient laboratory as described in detail elsewhere (23,24). Plasma creatinine concentration was determined at baseline and at 6-months intervals. Since creatinine measurements were made using the Jaffe method until November 2011 in our institution, glomerular filtration rate (GFR) was estimated by the conventional Schwartz formula (25) for data obtained until this period. After November 2011, creatinine was measured using the IDMS traceable method. Therefore, the modified Schwartz formula (26) was adopted to estimate GFR.

Outcomes. The end-points for this study were time from baseline until the occurrence of (1) CKD stage ≥ 3 and (2) ESRD or CKD stage 5. CKD was classified according to the stages proposed by the National Kidney Foundation practice guidelines (27). CKD stage 5 was defined as eGFR < 15 ml/min in three consecutives tests and/or the need for renal replacement therapy.

Covariates. The following variables were included in the analysis: period of admission (1970-1989 vs. 1990-2015), clinical presentation (antenatal vs. postnatal), presence of VUR, VUR laterality (unilateral vs. bilateral), baseline creatinine, baseline GFR, nadir creatinine (lowest creatinine during the first year after surgical intervention), UTI episodes, primary surgical intervention. Two time-dependent covariates were included in the analysis: proteinuria and hypertension.

Definitions. UTI was defined as growth of at least 100,000 cfu/ml in urine obtained by bag or from a mid-stream sample, with fever (38.0°C or more) and/or urinary symptoms. Hypertension was defined as values persistently above the 95^{th} percentile for age, gender, and height on three consecutive visits. Blood pressure measurements were performed as recommended by the Working Group of the National High Blood Pressure Education Program. Reference values and definitions of normal blood pressure were based on The Fourth Report on High Blood Pressure in Children and Adolescents

(28,29). For patients above 17 years of age, we considered as sustained hypertension values consistently above 140/90 mmHg. The presence of proteinuria was considered when urinary protein creatinine ratio is above 0.2 or 24-hour protein excretion is higher than 150 mg/day in at least two consecutive evaluations.

Statistical analysis. The values were expressed as medians and interquartile ranges (IQs) or means and SDs when appropriate. Potential prognostic variables were evaluated as predictors of survival in both time-fixed and time-dependent Cox models. In the time-fixed model, only the covariables presented until the first 12 months of life were applied. Univariate analysis was performed to identify variables that were significantly associated with adverse outcome. Univariate analyses were performed using the Kaplan-Meier nonparametric survival function estimator. Differences between dichotomous variables were assessed by the two-sided log-rank test (30). For the purpose of plotting the survival curves, the optimal cut-off point for continuous variables was determined by the receiver operating characteristic curve using the Youden index (31). Cox's regression model was applied to identify variables that were independently associated with adverse outcome. Only those variables that were found to be associated with adverse outcome by univariate analysis ($p < 0.25$) were included in Cox's regression model. Variables that met this criterion were included in the multivariable model. Inclusion in the final model was determined by a backward stepwise process with the use of the likelihood ratio to evaluate the effect of omitting variables. Values of $p<0.05$ were considered significant and 95% confidence intervals were provided when appropriate. Next, we fitted a multivariable time-dependent Cox model, including the time-dependent covariates. Variables selected for multivariable analyses were used to build a final model after checking for interactions and proportionality assumptions. Possible interactions between variables that remained in the final model were evaluated, including interaction terms in the model (32-34).

Development of clinical predictive model. A prognostic model was then constructed from these data by dividing each β coefficient in the final multivariable model with significant risk factors by the lowest β coefficient. The β coefficients were used for factor weighting; points were assigned to each independent prognostic factor, their coefficients being rounded to the nearest integer (35,36). Finally, a prognostic score was calculated for each patient by summing up the points. The prognostic score derived was then grouped into three categories (low, medium, and high-risk groups). We assessed

the accuracy of the derived model by looking at the components of accuracy (i.e., discrimination and calibration) (35-38). Discrimination was evaluated on the basis of 2, 5, and 10 years of follow-up using the *c* statistic, which represents the area under the receiver operating characteristic curve (for which larger values indicate better discrimination) (39). Calibration was also assessed graphically by a KM plot for patients in different risk groups (low-risk, medium-risk, and high-risk) (40-42). To adjust for overfitting and overoptimistic performance of the model, we performed an internal validation of our model with a bootstrapping technique (39). In each bootstrap sample, the entire modeling process was repeated, resulting in shrinkage of the regression coefficients when applicable (35,38,43). The shrinkage factor obtained from bootstrap results was 0.8958. All reported p values are two sided, and a p value <0.05 was considered to represent a statistically significant difference for all analyses including interaction terms.

Ethical aspects. The study was approved by the Ethics Committee of UFMG and the parents or legal guardians responsible for the children gave written informed consent to participate.

RESULTS

Baseline findings.

The main baseline clinical characteristics of 173 patients included in the analysis are summarized in Table 1. The median age of admission was 8.5 months (IQ range, 1.1 – 42.9) and 62 (35.8%) infants were diagnosed in the investigation of antenatal sonography abnormalities. Seventy-nine patients (45.6%) were followed up for more than 5 years and 55 (32%) for more than 10 years. The commonest primary surgical intervention was transurethral ablation of the valves in 98 patients (56.6%) and 6 infants (3.5%) died in neonatal period before any surgical intervention.

Table 1

Outcomes

Mean follow-up time was 83 months (SD, 70 months) for those patients who survived neonatal period. Thirty-six patients (20.8%) presented blood pressure persistently above the 95th percentile, according to age, gender, and height. It was estimated that the incidence of hypertension was about 12%, 21%, and 40% after 5, 10,

and 18 years after admission, respectively. Seventy-eight patients (45%) exhibited proteinuria. Similarly, the estimated incidence of proteinuria increased with age: 26%, 40%, and 70% after 5, 10, and 18 years after admission, respectively. At the end of follow-up, 80 patients had CKD stage 1 (46.2%), 28 (16.2%) patients, CKD stage 2, 16 (9.2), CKD stage 3, 10 (5.8%) CKD stage 4, and 39 (22.5%) reached CKD stage 5 or ESRD. Therefore, 65 children (37.6%) developed CKD stage ≥ 3 with a median GFR of 25.6 ml/min per 1.73 m2 (IQ, 12.4 – 38.0). Using Kaplan-Meier curves, the cumulative incidence of CKD stage ≥ 3 was estimated as about 24% at 5 years age, 37% at 10 years age, and 56% at 18 years age. In addition, the cumulative incidence of CKD stage 5 was estimated as about 10% at 5 years age, 15% at 10 years age, and 31% at 18 years age. Of 39 with CKD stage 5, 1 died within the first days of life, 28 were on dialysis, and 10 of them underwent renal transplantation. The laboratory evaluation at the end of follow-up revealed a median serum creatinine of 0.7 mg/dl (IQ, 0.45–0.89) for patients at CKD stages 1 and 2. The median estimated GFR for these patients was 100.4 ml/min per 1.73 m^2 (IQ, 83.3–120.1). During follow-up, UTI occurred in 148 (85.5%) children: 35 children (20.2%) presented one UTI episode, 25 (14.5%) had two episodes, and 88 (50.8%) children had three or more episodes. Of 173 patients included in the analysis, 14 (8.1%) died during follow-up. The median age at death was 2.7 months (IQ, 15 days – 66 months). The proportion of death was greater among patients enrolled in the first period of the study (14% vs. 5.7% for 1970-1989 and 1990-2015, respectively), but the difference was not statistically significant (OR=2.7, CI 95%, 0.89-8.14, P=0.07).

Univariate analysis

In univariate analysis, patients who evolved to CKD stage 3 or higher presented significantly more proportion of bilateral VUR, hypertension and proteinuria. These patients also had higher values of baseline serum creatinine and of nadir creatinine as well as lower values of eGFR (Table 2). Similarly, the same variables were associated with patients who evolved to CKD stage 5 (Table 3). Figure 1A-C illustrates the renal survival of CKD stage ≥ 3, according to the presence of bilateral VUR, baseline creatinine (cut-off 0.85 mg/dl), and nadir creatinine (cut-off 0.70 mg/dl).

Table 2

Table 3

Figure 1 (A-C)

Multivariate analysis

End-point CKD ≥ stage 3. As shown in Table 2, in univariate survival analysis, six variables were suitable for inclusion in the time-fixed multivariable model: VUR bilateral, proteinuria, hypertension, serum creatinine, nadir creatinine, and eGFR. The model derived from the time-fixed approach is displayed in Table 4. After adjustment, three variables were found to be independent predictors of CKD ≥ stage 3: baseline serum creatinine, nadir creatinine, and proteinuria. There was no interaction between the remained variables in the final model. The model derived from the time-dependent approach is given in Table 5. After adjustment by the Cox time-dependent model, four variables were found to be independent predictors of CKD ≥ stage 3: baseline creatinine, nadir creatinine, hypertension, and proteinuria. There was no interaction between the remaining variables in the final model.

Table 4

Table 5

End-point CKD stage 5 (ESRD). As shown in Table 3, the same six variables were also suitable for inclusion in the time-fixed multivariable model: VUR bilateral, proteinuria, hypertension, serum creatinine, nadir creatinine, and eGFR. The model derived from the time-fixed approach is shown in Table 6. Similarly, after the adjustment, three variables were found to be independent predictors of CKD stage 5: baseline serum creatinine, nadir creatinine, and proteinuria. There was no interaction between the remained variables in the final model. The model derived from the time-dependent approach is given in Table 7. After adjustment by the Cox time-dependent model, three variables were found to be independent predictors of CKD stage 5: nadir creatinine, hypertension, and proteinuria. There was no interaction between the remaining variables in the final model.

Table 6

Table 7

Clinical predictive model

A clinical predictive model based on a time-fixed Cox regression analysis was developed for the end-point CKD ≥ stage 3. A prognostic weighting was derived for each variable by dividing each β coefficient by the lowest β (Table 4). Finally, a prognostic risk score was calculated as the sum of these weightings for the three variables. A risk score was calculated for each patient by adding up these points. The risk score ranged from 0 to 79 points (median, 5 points). Finally, the prognostic risk score was divided into three categories: low-risk (≤3 points, 69 children, 39.9%), medium-risk (4–20 points, 45, 26%), and high-risk (> 20 points, 59, 34.1%) for the event. The accuracy of the score applied to the sample was consistently high through time, with a mean *c* statistic of 0.867 (95%CI, 0.804–0.916), 0.838 (95%CI, 0.729–0.916), and 0.847 (95%CI, 0.766–0.909) for the follow-up periods of 2, 5, and 10 years, respectively (Figure 2A-C). The accuracy of the model was also assessed by the Kaplan-Meier method (Figure 3). The probability of CKD ≥ stage 3 at 10 years age was estimated as 6%, 40%, and 70% for patients assigned to the low-risk, medium-risk, and high-risk groups, respectively ($P < 0.001$).

Figure 2 (A-C)

Figure 3

DISCUSSION

In this retrospective cohort study, we evaluated clinical outcome and risk factors for CKD in a cohort of children with PUV. Our findings confirm the dismal prognosis for the renal function among children with PUV. According to our analysis, about half of these patients evolved to moderate to severe renal function impairment and about a third of them will need renal replacement therapy at about 18 years of age. Interestingly, we also identified baseline serum creatinine, nadir creatinine, hypertension, and proteinuria as possibly predictive factors of CKD during follow-up in this population.

The mortality rate in patients with PUV has significantly decreased in the past decades, from 50% to less than 5% (44-46). In our study, the overall mortality was 8.1% in agreement with recent published series (10). Nevertheless, the survival rate has improved in the last period of the study (5.7%), possibly due to multiple factors

including early diagnosis, improvement of respiratory support, and better management of renal impairment in neonates and infants. Moreover, during the first years of our cohort, renal replacement therapy for infants had not been fully implemented at our institution. However, during the study period, a Predialysis Interdisciplinary Management Program was created in our Unit with the aim to provide full clinical assistance to children with CKD (47). We believe that this program has contributed to improving the prognosis for these patients (48,49).

The decrease in mortality rate has resulted in more patients facing the long-term sequelae of PUV during puberty and adulthood, including renal function impairment and bladder dysfunction (16, 50, 51). In our series, the rate of moderate to severe CKD was 37.5% (65/173) and 22.5% (39/173) patients reached ESRD. Of note, the cumulative incidence of CKD ≥ stage 3 and of CKD stage 5 was estimated, respectively, as about 56% and 31%, at 18 years age. It is not a trivial task to compare these data with the literature on PUV, since the modern concept of CKD and its classification was established only on the beginning of 2000s (27). Before this era, there were several different classifications for the so-called chronic renal insufficiency and this scenario hampers the comparison and interpretation of clinical studies concerning this issue. Consequently, the rate of progression to CKD and/or to ESRD in patients with PUV varies widely from 22% to 68% across a number of studies (45,52-54). Nevertheless, current series have shown renal outcome quite similar to our series. For instance, Ylinen et al(55) have shown in a series of 46 boys that the long-term renal outcome was poor in 14 (30%) after a mean follow-up period of 12.5 years. From a large cohort with a long term follow-up of 193 patients, Heikkilä et al(16) have reported that 44 (22.8%) patients progressed to ESRD. Interestingly, Kaplan-Meier analysis estimated that the lifetime risk of ESRD in this series was 28.5%, again quite similar to our sample. Sarhan et al (56) evaluated 120 patients with PUV using the same definitions of CKD used in our study. Follow-up time was from 2 to 16 years with a median of 3.6 years. CKD stages 3 to 5 developed at the end of follow-up in 44 patients (36.5%) and ESRD in 18 (15%).

A number of studies have evaluated risk factors associated with a poorer renal outcome in PUV. However, the majority of these studies have applied univariate analysis or included only baseline variables in the analysis. From our point of view, the strength of the present study relies on the inclusion of well-recognized factors

associated with long-term impairment of the renal function, namely proteinuria and hypertension in a time-dependent Cox regression model. Of note, both time-dependent variables remained as predictive factors for renal function impairment in our series.

Several studies have identified possible predictive factors associated with the development of ESRD in patients with PUV, including oligohydramnios, baseline creatinine concentration, nadir serum creatinine after a period of decompression, need of ventilatory support, bilateral vesicoureteral reflux (VUR), delayed diagnosis, bladder dysfunction, delayed achievement of urinary continence, and breakthrough urinary tract infections (21,52-55, 58-65). Recently, Pulido et al. (66) have shown that a reduced renal parenchymal area as observed on the first postnatal ultrasound is associated with an increased risk of ESRD during childhood. On the other hand, factors including unilateral VUR, large congenital bladder diverticula, and urinary extravasation are considered as protective factors (67).

We believe that the most original contribution of our study was the demonstration of the role of hypertension and proteinuria in the progression of CKD in children with a congenital anomaly of kidney and urinary tract (CAKUT). As a matter of fact, there have been a number of studies in adults and children showing that both, hypertension and proteinuria, are consistently associated with decline of the renal function in diverse clinical conditions (68-74). For instance, in the context of CAKUT, Ardissino et al (75) have shown that proteinuria is an independent predictor of progression to ESRD in children with congenital hypodysplastic kidneys. Similarly, Fathallah-Shaykh et al (68) have reported that baseline proteinuria and systolic BP levels are independently associated with CKD progression in 522 children with non-glomerular CKD enrolled in the CKiD study. Nevertheless, to the best of our knowledge, our study is the first to show, by a time-dependent model, the importance of hypertension and proteinuria, both potential modifiable factors, in the progression of renal function impairment in children with PUVs. These findings indicate the need of more active investigation and more aggressive clinical intervention in modifiable factors in order to slow the decline of renal function in PUV. In this regard, the ESCAPE trial has shown that an intensified blood-pressure control confers a substantial benefit with respect to renal function preservation among children with CKD (76).

The retrospective nature of our study is a clear limitation. Possibly, the main weakness is related to the impossibility to recover some important data from the records

of the patients. Thus, we were unable to analyze variables including prematurity, birth weight, and sonography renal measurements, all of which may contribute to the prediction of renal outcome of children with PUV. On the other hand, we believe that the most original aspect of our study was the systematic analysis of clinical outcome in this selected group of infants and the evaluation of time-dependent covariables as risk factors for renal function impairment in a large cohort of patients with VUP. In addition, the size of our sample, the length of the follow-up time, and the management by the same medical team using a standardized protocol might minimize the biases inherent to longitudinal cohort studies.

In summary, in this retrospective cohort study, we observed that, in spite of recent advances in the management of PUV, the renal outcome did not improve for the majority of patients. Nevertheless, our findings stress the importance of earlier identification of risk factors amenable to clinical intervention that can possibly contribute to slow the rate of renal impairment. If confirmed in future studies, infants with PUV may benefit from closer surveillance for proteinuria and hypertension during follow-up. Further prospective studies and clinical trials are obviously necessary to establish the best interventions for these modified factors in children with PUVs and to propose a tailored therapeutic approach.

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Conflicts of interest. none

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Table 1 - Baseline clinical characteristics of 173 infants with PUV, Pediatric Nephrology Unit, 1970-2015

	N (%)
Diagnosis	
Antenatal	62 (35.8)
Postnatal	111 (64.2)
Period	
1970 – 1989	50 (28.9)
1990 - 2015	123 (71.1)
Age of admission (months)	
Median (IQ range)	8.5 (1.1 – 42.9)
VUR features	
Absent	61 (35.3)
Unilateral	45 (26.0)
Bilateral	67 (38.7)
Primary Surgical Intervention	
Vesicostomy	54 (31.2)
Suparevesical diversion	15 (8.70)
Transurethral ablation	98 (56.6)
None	6 (3.50)
Creatinine (mg/dl)	
Median (IQ range)	0.86 (0.50 – 1.6)
GFR (ml/min/1.73m^2)	
Median (IQ range)	42 (18.9 – 72.2)
Nadir Creatinine (mg/dl)	
Median (IQ range)	0.6 (0.40 – 1.09)

Table 2 - Univariate analysis of risk factors for CKD ≥3 in children with PUV (n=173), Pediatric Nephrology Unit, 1970-2015.

Variables	CKD < 3 n = 108 (%)	CKD ≥ 3 n = 65 (%)	p-value*
Diagnosis			
Prenatal	41 (66.1)	21 (33.9)	0.83
Postnatal	67 (60.4)	44 (39.6)	
Period of admission			
1970 – 1989	28 (56.0)	22 (44.0)	0.76
1990 - 2015	80 (65.0)	43 (35.0)	
VUR			
Absent	42 (68.9)	19 (31.1)	0.19
Unilateral	30 (66.7)	15 (33.3)	
Bilateral	36 (53.7)	31 (46.3)	
VUR			
Absent/Unilateral	72 (67.9)	34 (32.1)	0.13
Bilateral	36 (53.7)	31 (46.3)	
Proteinuria			
Absent	100 (65.8)	52 (34.2)	<0.001
Present	8 (38.1)	13 (61.9)	
Hypertension			
Absent	106 (62.7)	63 (37.3)	0.028
Present	2 (50.0)	2 (50.0)	
UTI episodes/year			
Median (IQ range)	0.49 (0.2 – 1.41)	0.44 (0.07 – 2.3)	0.78
Creatinine (mg/dl)			
Median (IQ range)	0.60 (0.40 – 1.01)	1.60 (0.92 – 3.0)	<0.001
GFR (ml/min/1.73m^2)			
Median (IQ range)	58.1 (27.2 – 84.5)	23.0 (12.0 – 39.5)	<0.001
Nadir Creatinine (mg/dl)			
Median (IQ range)	0.47 (0.31 – 0.60)	1.20 (0.88 – 1.70)	<0.001

Table 3 - Univariate analysis of risk factors for CKD Stage 5 in children with PUV (n=173), Pediatric Nephrology Unit, HC/UFMG, 1970-2015

Variables	CKD 1-4 n = 135 (%)	CKD 5 n = 38 (%)	p-value*
Diagnosis			
Prenatal	49 (79.0)	13 (21.0)	0.29
Postnatal	86 (77.5)	25 (22.5)	
Period of admission			
1970 – 1989	38 (76.0)	12 (24.0)	0.63
1990 - 2015	97 (78.9)	26 (21.1)	
VUR			
Absent	52 (85.2)	9 (14.8)	
Unilateral	37 (82.2)	8 (17.8)	0.09
Bilateral	46 (68.7)	21 (31.3)	
VUR			
Absent/Unilateral	89 (84.0)	17 (16.0)	0.03
Bilateral	46 (68.7)	21 (31.3)	
Proteinuria			
Absent	124 (81.6)	28 (18.4)	<0.001
Present	11 (52.4)	10 (47.6)	
Hypertension		36 (21.3)	<0.001
Absent	133 (78.7)	2 (50.0)	
Present	2 (50.0)		
UTI episodes/year			
Median (IQ range)	0.47 (0.18 – 1.7)	0.55 (0.07 – 1.7)	0.47
Creatinine (mg/dl)			
Median (IQ range)	0.7 (0.49 – 1.2)	2.0 (1.5 – 3.4)	<0.001
GFR (ml/min/1.73m^2)			
Median (IQ range)	51.6 (25.2 – 75.5)	15.4 (8.0 – 31.4)	<0.001
Nadir Creatinine (mg/dl)			
Median (IQ range)	0.50 (0.35 – 0.73)	1.52 (1.2 – 2.0)	<0.001

Table 4 - Risk factors associated with CKD ≥ 3 after adjustment by the Cox regression model without time-dependent covariables and respective weighting points used in the risk score, Pediatric Nephrology Unit, HC/UFMG, 1970-2015.

Variables	**Coefficient***	**Hazard Ratio (95% CI)**	**p value**	***Points***
Baseline creatinine (mg/dl)	0.210	1.23 (1.09-1.88)	<0.001	
0,20 – 0,49				0
0,50 – 0,70				1
0,71 - 1,10				2
1,11 – 1.80				4
≥1,81				20
Nadir creatinine (mg/dl)	0,234	1.260 (1.11 – 1.43)	<0.001	
0.13 – 0.37				0
0.38 - 0.50				1
0.51 – 0.74				2
0.75 – 1.21				4
≥1,22				28
Proteinuria at baseline	1.378	3.96 (2.10 – 7.47)	<0.001	31

Table 5 - Risk factors associated with CKD ≥ 3 after adjustment by the Cox regression model with time-dependent covariables , Pediatric Nephrology Unit, HC/UFMG, 1970-2015

Variables	Coefficient	Hazard Ratio (95% CI)	p value
Baseline creatinine (mg/dl)	0.216	1.14 (1.01-1.28)	0.04
Nadir creatinine (mg/dl)	0.27	1.31 (1.17 – 1.48)	<0.001
Hypertension	1.51	4.54 (2.10 – 9.91)	<0.001
Proteinuria	1.46	4.30 (2.30 – 8.06)	<0.001

Table 6 - Risk factors associated with CKD 5 after adjustment by the Cox regression model without time-dependent covariables, Pediatric Nephrology Unit, HC-UFMG, 1970-2015

Variables	Coefficient	Hazard Ratio (95% CI)	p-value
Baseline creatinine (mg/dl)	0.221	1.24 (1.09-1.42)	0.001
Nadir creatinine (mg/dl)	0.325	1.38 (1.21 – 1.58)	<0.001
Proteinuria	1.822	6.18 (2.84 – 13.47)	<0.001

Table 7 - Risk factors associated with CKD 5 after adjustment by the Cox regression model with time-dependent covariables, Pediatric Nephrology Unit, HC/UFMG, 1970-2015

Variables	**Coefficient**	**Hazard Ratio (95% CI)**	**p-value**
Nadir creatinine (mg/dl)	0.36	1.44 (1.26 – 1.63)	<0.001
Hypertension	1.22	3.40 (1.45 – 7.90)	0.005
Proteinuria	3.11	22.44 (9.14 – 55.04)	<0.001

FIGURES:

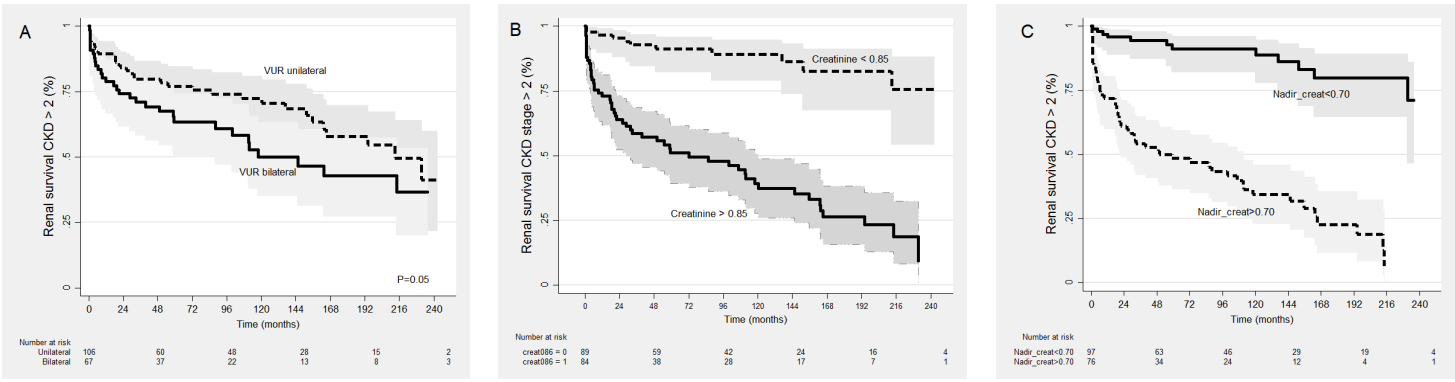

Figure 1 - Kaplan-Meier curves showing the probability of CKD≥3 according to (A) presence of bilateral VUR, (B) baseline creatinine, and (C) nadir creatinine, Pediatric Nephrology Unit, HC/UFMG, 1970-2015.

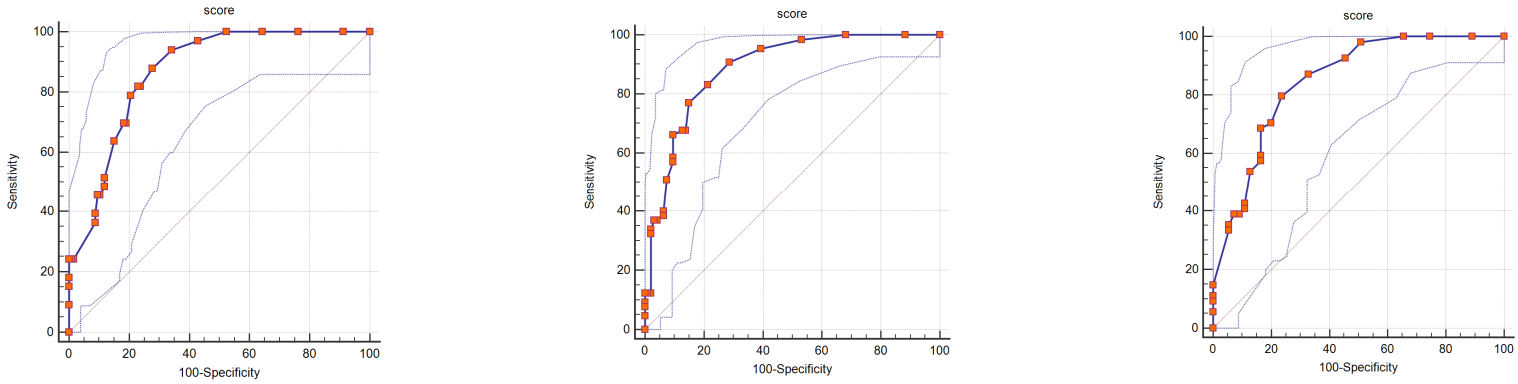

Figure 2 - Receiver Operating Characteristic Curve Risk Score of CKD ≥ 3 according to follow-up time. (a) 2 years follow-up (*c* statistic: 0.867 - 95%CI, 0.804–0.916); (b) 5 years follow-up (*c* statistic 0.838 - 95%CI, 0.729–0.916) (c) 10 years follow-up (*c* statistic 0.847- 95%CI, 0.766–0.909).

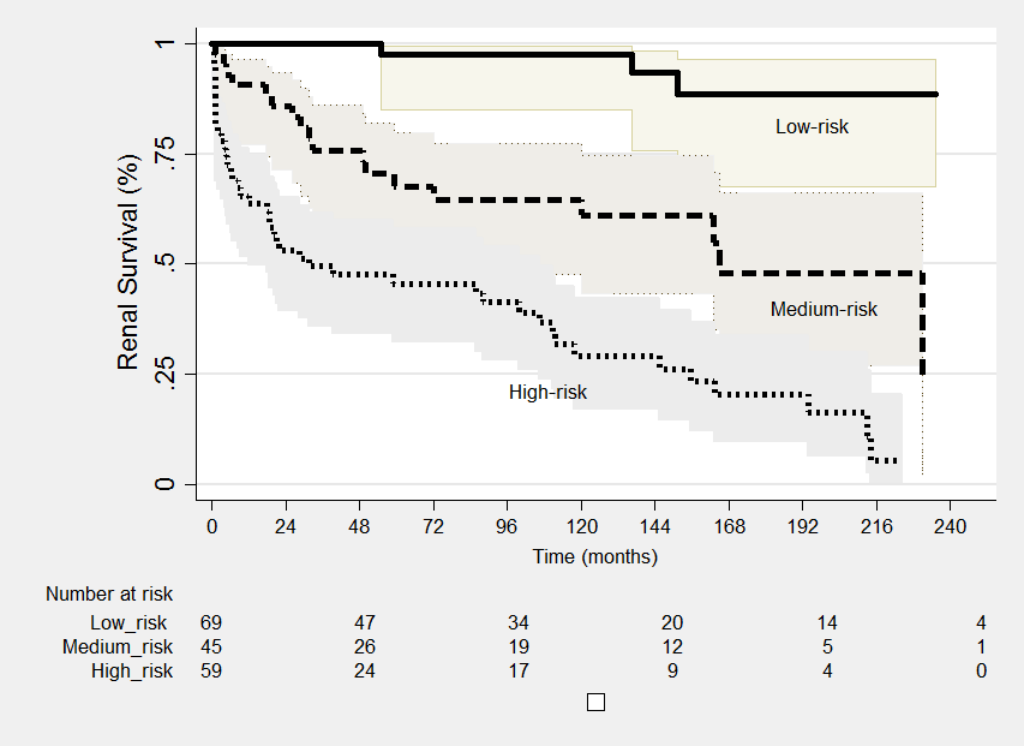

Figure 3 - Kaplan-Meier curves showing the probability of CKD ≥3 according to risk groups derived from the clinical predictive model

6. CONSIDERAÇÕES FINAIS E CONCLUSÕES

Apesar dos crescentes avanços diagnósticos e genéticos nos últimos anos em CAKUT, ainda existem muitas lacunas a serem preenchidas com relação ao manejo dos pacientes portadores dessas anomalias (1-5). A presente tese consistiu na avaliação retrospectiva de duas coortes de pacientes com CAKUT, na qual abordamos (1) aspectos da necessidade de cirurgia e os fatores preditivos deste evento, e (2) um aspecto mais específico, a evolução para DRC, moderada a grave, de pacientes com VUP. Em ambas análises foram desenvolvidos modelos de predição clínica para os eventos estudados.

O manejo de pacientes com CAKUT ainda apresenta controvérsias sobre a forma de abordagem mais conservadora ou mais agressiva. A avaliação propedêutica pode ser bastante extensa, invasiva e de alto custo ocasionando impacto significativo nos sistemas de saúde público e privado. Além disso, o diagnóstico de CAKUT pode causar significativa ansiedade nos pais e incerteza médica, no que concerne principalmente ao tratamento pré-natal e pós-natal (6). A tendência atual tem sido uma abordagem mais conservadora em substituição à intervenção cirúrgica (7-10). Frente a esta situação, o objetivo do primeiro estudo foi detectar variáveis preditivas para necessidade de cirurgia em pacientes com CAKUT. A partir daí, o desenvolvimento de um modelo de predição para a necessidade de cirurgia. O modelo de predição é uma ferramenta que tem como objetivo auxiliar o médico na conduta de pacientes direcionando sua atenção para os que possuem maior risco para o tratamento cirúrgico. Este estudo, as variáveis preditivas fortemente associadas à necessidade de cirurgia foram: ritmo de filtração glomerular reduzido, anomalias do trato urinário associadas à dilatação da pelve renal, presença de lesões renais ao DMSA e a magnitude da dilatação da pelve renal. Foi desenvolvido modelo de predição com uma boa acurácia, estatística *c de* 0.84 (IC 95% 0.82-0.87). O instrumento utilizado para apresentar o modelo foi o nomograma, pois trata-se de uma excelente ferramenta para ser utilizada na rotina médica por sua facilidade de manejo. No entanto, é importante ressaltar que é necessária a validação externa do modelo com outras séries de CAKUT.

Em relação ao segundo estudo, abordamos a evolução para DRC de pacientes com VUP. Apesar de rara, a VUP é uma doença que gera alta morbidade em pacientes com CAKUT (11-15). Neste estudo, encontramos como variáveis preditivas para

ocorrência de DRC estágio ≥ 3 e DRC estágio 5 nadir de creatinina, ritmo de filtração glomerular estimado à admissão, hipertensão arterial (HAS) e proteinúria. Deve ser ressaltado que trabalhamos os cofatores hipertensão arterial e proteinúria como variáveis tempo-dependentes, pois são reconhecidamente fatores que podem variar com o tempo de seguimento do paciente. Importante ressaltar ainda que não existem estudos na literatura que abordam variáveis tempo-dependentes como as duas últimas. E finalmente, desenvolvemos um modelo de predição com variáveis fixas coletadas no primeiro ano de admissão do paciente. Neste modelo, foram significativas as covariávies: nadir de creatinina, ritmo de filtração glomerular estimado à admissão e proteinúria. Esse modelo apresentou excelente acurácia para 2, 5 e 10 anos de seguimento, estatística *c* de 0.867 (95%CI, 0.804–0.916), 0.838 (95%CI, 0.729–0.916) e 0.847 (95%CI, 0.766–0.909), respectivamente. Estes achados demonstram a importância de identificar fatores de risco responsáveis pela perda da função renal, possibilitando a intervenção clínica precoce e possivelmente reduzindo a velocidade da progressão da DRC.

7. PROPOSTAS DE INVESTIGAÇÃO FUTURA

Diante das considerações acima delineadas, é evidente que novos estudos se fazem necessários para esclarecer diversas dúvidas que permeiam a questão do diagnóstico e evolução dos pacientes e crianças portadoras do complexo CAKUT. Alguns possíveis estudos são pontuados a seguir:

- Modelos de predição clínica incorporando variáveis, como marcadores ecográficos e biológicos, tais como espessura do parênquima renal, volume renal, prematuridade, baixo peso ao nascimento, obesidade e variáveis tempo-dependentes, como hipertensão e proteinúria.
- Validação externa dos modelos preditivos de necessidade de cirurgia e desenvolvimento de DRC;
- Avaliar questões pertinentes aos modelos de predição clínica, como extensão, calibração e validação.
- Avaliar modelos de predição incorporando covariáveis tempo-dependentes.
- Estudo de novos biomarcadores urinários e séricos que possam predizer alguns desfechos, como obstrução significativa do trato urinário, deterioração da função renal e hipertensão arterial.
- Estudo de marcadores genéticos, como polimorfismos e mutações possivelmente mais prevalentes nesta população, que possam auxiliar na compreensão da ontogênese do complexo CAKUT e, consequentemente, contribuir para aconselhamento genético e tratamento individualizado para esses pacientes.

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8. APENDICE

Original article

Antenatal diagnosis of posterior urethral valves: impact in long-term clinical outcomes

Running title: Outcome of posterior urethral valves

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ABSTRACT

Background and objectives: Posterior urethral valves (PUV) constitute the most common infravesical urinary obstruction in boys and are often accompanied by severe consequences to the lower and upper urinary tract. The aim of this study was to evaluate the impact of antenatal diagnosis on long-term clinical outcome of patients with PUV.

Design, setting, participants, & measurements: In this retrospective cohort study, 173 patients with PUVs stratified according to the clinical presentation (prenatal vs. postnatal) were systematically followed up at a tertiary Renal Unit for a mean time of 83 months. The events of interest were urinary tract infection (UTI), surgical interventions, proteinuria hypertension, chronic kidney disease (CKD), and death. Survival analyses were performed in order to evaluate time until occurrence of the events of interest.

Results: 62 patients (35.8%) were diagnosed by fetal sonography. Patients of postnatal group presented a higher risk of UTI episodes (OR = 10.0, 95%CI, 3.5 – 28.6, P<0.01) as well as of recurrent UTIs (OR = 5.6, 95%CI, 2.8 – 11.2). Thirty-six patients (21%) presented hypertension and 77 (44.5%) presented persistent mild proteinuria. By survival analysis there was no significant difference in the estimated incidence of hypertension (Log rank= 1.1, P = 0.28) and proteinuria (Log rank= 0.09, P = 0.78) between antenatal and postnatal groups. The cumulative incidence of CKD stage ≥ 3 was estimated as about 37% at 10 years age, and 56% at 18 years age. By survival analysis there was also no significant difference in the estimated incidence of CKD stage ≥ 3 (Log-rank=0.32, P = 0.57) and CKD stage 5 (Log rank= 1.08, P = 0.28) between the groups.

Conclusion: Our study suggests that, for severe kidney and urinary tract anomalies such as PUV, the renal outcome has not been improved with early diagnosis and management.

INTRODUCTION

Posterior urethral valves (PUVs) constitute the most common infravesical urinary obstruction in boys with an estimated incidence of 1 per 3,000 to 8,000 live birth(1), with a disproportionately elevated incidence in African-Americans and infants with Down's syndrome (2). Lloyd et al.(3) reported a weighted prevalence rate of 9.3 PUV births per 100,000 in-hospital live male births in USA. PUVs are often accompanied by severe consequences to the lower and upper urinary tract (4, 5). While the mortality rate in patients with PUVs has significantly decreased in the past decades, approximately a quarter of the patients present progression to ESRD during a long-term follow up (6, 7).

Over the last two decades, antenatal ultrasound evaluation of the developing fetus has become routine care in the management of healthy pregnancies (8). Consequently, congenital anomalies of kidney and the urinary tract (CAKUT), including PUVs, has been diagnosed in utero (9-11). Two-thirds of infants with PUVs have been identified by prenatal US in the developed world (12). Nevertheless, to our knowledge the long-term impact of prenatal diagnosis of PUV has not been systematically assessed. Moreover, studies comprising a systematic analysis of the clinical outcomes of PUVs are scarce, which might provide further insight into unresolved issues. The aim of this study was to evaluate the impact of prenatal diagnosis of PUV by comparing two cohorts treated at tertiary centre between 1970 and 2015.

MATERIALS AND METHODS

Patients. In this retrospective cohort study, the records of 178 patients with PUVs who were admitted consecutively at the Pediatric Nephrourology Unit of Hospital das Clinicas of Federal University of Minas Gerais (UFMG, Brazil) between 1970 and 2015 were reviewed. Patients were stratified into two groups according to the clinical presentation (antenatal vs. postanatal diagnosis). We excluded five patients from the analysis due to lost to follow-up.

Baseline data. All patients were admitted to our outpatient facility. For the antenatal cohort, after the initial renal and bladder US (RBUS), neonates with antenatal hydronephrosis suspect of PUV underwent urinary tract imaging workup according to a systematic protocol described in detail elsewhere (13, 14). Antibiotic prophylaxis was

started at the first postnatal day and maintained according to the specific uropathy. For the postnatal cohort, the majority of the cases were diagnosed in the context of the investigation after an episode or recurrent episodes of febrile UTI as described in detail elsewhere (15, 16). The presence of PUV and associated vesicoureteral reflux (VUR) was ascertained by independent radiologists after conventional voiding cystourethrography.

Follow-up protocol. After initial evaluation and surgical intervention, clinical, laboratory and imaging assessments were carried out periodically at 6-month intervals. Briefly, the clinical approach consisted of full physical examination, including evaluation of anthropometric measurements and blood pressure performed at 6-month intervals or more frequently whether clinically needed. Urine cultures were obtained at each follow-up visit, and it was recommended that urine samples should be collected during any unexplained febrile episode or in the presence of urinary symptoms. Urine specimens for culture were carefully collected at our hospital outpatient laboratory as described in detail elsewhere (17, 18). Plasma creatinine concentration was determined at baseline and yearly thereafter. Since creatinine measurements were made using the Jaffe method until November 2011 in our institution, glomerular filtration rate (GFR) was estimated by the conventional Schwartz formula (19) for data obtained until this period. After November 2011, creatinine was measured using the IDMS traceable method. Therefore, the modified Schwartz formula (20) was adopted to estimate GFR.

Outcomes. The events of interest were surgical interventions, UTI, hypertension, proteinuria, chronic kidney disease (CKD) ≥3 , ESRD, and death.

Covariates. The following variables were included in the analysis: period of admission (1970-1989 vs. 1990-2015), presence of VUR, VUR laterality (unilateral vs. bilateral), baseline creatinine, baseline glomerular filtration rate (GFR), nadir creatinine (lowest creatinine during the first year after surgical intervention), primary surgical intervention, dysfunctional voiding (including daytime and/or nighttime urinary incontinence)

Definitions. CKD was classified according to the stages proposed the National Kidney Foundation practice guidelines (21). Urinary tract infection (UTI) was defined as growth of at least 100,000 cfu/ml in urine obtained by bag or from a mid-stream sample, with fever (38.0°C or more) and/or urinary symptoms. Hypertension was defined as values persistently above the 95th percentile for age, gender, and height on three consecutive visits. Blood pressure measurements were performed as recommended by the Working Group of the National High Blood Pressure Education Program. Reference

values and definitions of normal blood pressure were based on The Fourth Report on High Blood Pressure in Children and Adolescents (22, 23). For patients above 17 years of age, we considered as sustained hypertension values consistently above 140/90 mmHg. The presence of proteinuria was considered when urinary protein creatinine ratio is above 0.2 or 24-hour protein excretion is higher than 150 mg/day in at least two consecutive evaluations.

Statistical analysis. The values are expressed as medians and interquartile range (IQ) or means and standard deviation (SD), when appropriate. The Mann-Whitney or Kruskal-Wallis test was used to compare nonparametric continuous variables. Odds ratio (OR) and 95% confidence intervals (95%CI) were used for group risk comparison. Survival analyses were performed by the Kaplan-Meier method with log-rank in order to evaluate time until occurrence of outcomes: CKD, hypertension, proteinuria, and death. Differences between groups were assessed by the two-sided log rank test.

Ethical aspects. The study was approved by the Ethics Committee of UFMG.

RESULTS

Baseline findings

A total of 173 patients were included in the analysis, 62 (35.8%) of them diagnosed prenatally. The main baseline clinical characteristics of these patients stratified according to the clinical presentation are summarized in Table 1. Children enrolled after 1990 had a 14 times greater chance to be detected prenatally compared to those admitted during the period between 1970 and 1989 (OR=14.4, 95%CI, 4.2–48.9, $p<0.001$). As expected, postnatal group was older and, consequently, presented higher median GFR at admission.

Table 1

Clinical course

Mean follow-up time was 83 months (SD, 70 months) for those patients who survived neonatal period. Seventy-nine (45.6%) patients were followed up for more than 5 years and 55 (32%) for more than 10 years.

Surgical interventions. The most common primary surgical interventions was transurethral ablation of the valves in 98 patients (56.6%). Fifty-four infants (31.2%) underwent vesicostomy and 15 patients (8.7%) had supravesical diversion on neonatal period as primary intervention. Six infants (3.5%) died in neonatal period before any surgical intervention. Postnatal group had significantly more transurethral ablation as

primary surgical intervention (Table 1). Of note, infants who underwent supravesical diversion presented a significant worse renal survival as shown in Figure 1. However, this subgroup presented higher levels of serum creatinine at admission (P=0.003).

Figure 1

Urinary tract infection. During follow-up, UTI occurred in 148 (85.5%) children. Approximately, half of the cohort (85, 49.1%) present two or less episodes while 88 children (50.9%) had three or more episodes. As can be seen in Table 2, patients of postnatal group presented a higher risk of UTI episodes (OR = 10.0, 95%CI, 3.5 – 28.6, P<0.01) as well as of recurrent UTIs (OR = 5.6, 95%CI, 2.8 – 11.2). This difference remained significant even after adjusted by the follow-up time (Table 2).

Table 2

Hypertension. Thirty-six patients (21%) presented blood pressure persistently above the 95th percentile according to age, gender, and height. The cumulative incidence of hypertension was estimated in about 12% at 5 years age, 18% at 10 years age, and 40% at 18 years age. The risk of hypertension was greater in postnatal group (OR = 2.7, 95%CI, 1.1 – 6.7, P = 0.02). Nevertheless, by survival analysis there was no significant difference in the estimated incidence of hypertension between antenatal and postnatal groups (Log rank= 1.1, P = 0.28) (Figure 2).

Figure 2

Proteinuria. Of 173 patients included in the analysis, 77 (44.5%) presented persistent mild proteinuria at an estimated median age of 163 months (IQ, 142 – 189 months). The cumulative incidence of proteinuria was estimated in about 27% at 5 years age, 40% at 10 years age, and 61% at 18 years age. The risk of proteinuria was also greater in postnatal group (OR = 1.9, 95%CI, 1.04 – 3.8, P = 0.035) (Table 2). However, again by survival analysis there was no significant difference in the estimated incidence of proteinuria between antenatal and postnatal groups (Log rank= 0.09, P = 0.78) (Figure 3).

Figure 3

Chronic kidney disease. At the end of follow-up, 80 patients had CKD stage 1 (46.2%), 28 (16.2%) patients, CKD stage 2, 16 (9.2), CKD stage 3, 10 (5.8%) CKD stage 4, and 39 (22.5%) reached CKD stage 5. Therefore, 65 children (37.6%) developed CKD stage $\geq$ 3 with a median GFR of 25.6.0 ml/min per 1.73 m^2 (IQ, 12.4 – 38.0). The cumulative

incidence of CKD stage ≥ 3 was estimated as about 24% at 5 years age, 37% at 10 years age, and 56% at 18 years age. By contrast, the cumulative incidence of CKD stage 5 was estimated as about 10% at 5 years age, 15% at 10 years age, and 31% at 18 years age. There was no significant difference between antenatal and postnatal groups regarding risk of CKD stage ≥ 3 (OR=1.3, CI95%, 0.67 – 2.4, P = 0.45) as well as of CKD stage 5 (OR = 1.09, CI95%, 0.51 – 2.3, P = 0.81). Similarly, by survival analysis there was no significant difference in the estimated incidence of CKD stage ≥ 3 (Log-rank=0.32, P = 0.57, Figure 4) and CKD stage 5 (Log rank= 1.08, P = 0.28, Figure 5) between antenatal and postnatal groups.

Of 39 with CKD stage 5, 1 died within the first days of life, 28 were on dialysis, and 10 of them underwent renal transplantation. The laboratory evaluation at the end of follow-up revealed a median serum creatinine of 0.7 mg/dl (IQ, 0.45–0.89) for patients who did not present CKD. The median estimated GFR for these patients was 100.4 ml/min per 1.73 m^2 (IQ, 83.3–120.1).

Figure 4

Figure 5

Death. Of 173 patients included in the analysis, 14 (8.1%) died during follow-up. The median age at death was 2.7 months (IQ, 15 days – 66 months). There was no significant difference between antenatal and postnatal groups regarding risk of death (OR=0.72, 95%CI, 0.24 – 2.2, P = 0.57). Survival analysis also have not shown any significant difference in the estimated incidence of death between antenatal and postnatal groups (Log-rank=1.03, P = 0.31, Figure 6).

Figure 6

DISCUSSION

In this retrospective cohort study we compared the clinical outcomes of two cohorts of children with PUV, stratified according to the clinical presentation. The main finding of our cohort is that the impact of an earlier diagnosis of PUV by antenatal sonography has not apparently improved the prognosis of these patients. The only benefit highlighted by our analysis was a less number of episodes of UTI in the patients prenatally detected. Nevertheless, is important to stress some difficulties with this sort of comparison of somehow distinct cohorts and the possibilities of bias inherent to this

analysis. Although many specific types of bias in cohort studies have been described, there are three broad categories: selection bias, information bias, and confounding(24). Particularly in our study, is important to comment some issues concerning to the selection bias. It is clear that there is a wide spectrum of outcome for patients with PUV. Moreover, there is a high mortality associated with urethral obstruction that is not reflected in the medical literature. This represents the so-called ‘‘hidden mortality’’ of this disorder, because the newborn may die before be transferred to a specialized pediatric center or even before the definitive diagnosis (25). Therefore, the former literature regarding the prognosis of children with PUV possibly overestimated the outcome of these patients since comprised of only those individuals who survived the perinatal period. Possibly, after the prenatal diagnosis, the current literature including all the spectrum of infants with PUV depicts more accurately the prognosis for this population. Another issue to be considered in our study is the occurrence of some cohort effect, i.e., variations resulting from the unique experience/exposure of a group of subjects (cohort) as they move across time. For instance, one might speculate that antenatal cohort could has been somehow benefited by the improvement on intensive perinatal care and by the advances of the treatment of renal failure in infants. Consequently, our results must be considered in light of these potential limitations inherently associated with cohort studies. On the other hand, we believe that the most original aspect of our study was the systematic analysis of clinical outcomes in children with PUVs. To the best of our knowledge, our study is the first to systematically evaluate covariables associated with for renal impairment such as proteinuria and hypertension in a large series of PUV. In addition, the size of our sample, and the management by the same medical team, and a long follow-up time might minimize the biases inherent to cohort studies.

At baseline, as expected the antenatal and postnatal groups differed concerning some variables, such age, period of enrolment, and primary surgical intervention. Interesting, the baseline creatinine of both groups has not differed significantly although the estimated GFR has been higher for the postnatal group possibly due to the greater age of admission. Regarding the events of interest as a whole, our analysis has shown that the clinical outcomes for antenatal and postnatal cohorts were quite similar. The only difference observed emerged from the analysis of UTI episodes through the follow-up. Interestingly, the postnatal group has presented a significant higher incidence of UTI even after adjustment by the length of the follow-up. We believe that multiple

factors could have contributed in reducing the incidence of UTI in the antenatal group, including the immediate use of antibiotic prophylaxis soon after birth. However, from our point of the view, this fact cannot account exclusively for this improvement. In spite of early antibiotic prophylaxis and careful follow-up, UTI has occurred at a significant rate in our series of antenatally detected hydronephrosis (11, 17). Therefore, probably other factors also had an adjuvant role in the prevention of UTI in the antenatal group, including a better understanding and management of dysfunction of the lower urinary tract that may follow the patients with PUV throughout life (26-29). Typically, these patients suffer from detrusor overactivity and a low compliance bladder in early childhood, and later the bladder may become hypoactive and distended (30-32). Thus, patients admitted later in our series, most with prenatal diagnosis, had the opportunity to receive an active urotherapeutic intervention as well as an early anticholinergic medication. Other factor that may have contributed to a smaller incidence of UTI was the improvement in the recognition and treatment of constipation intestinal, which was certainly undervalued in the earlier period of our series. Moreover, the retrospective nature of our study has precluded to recover reliable information concerning dysfunctional elimination syndrome, urinary continence, and other important features that were not systematically obtained before 1990 as they are today (26, 28, 29). In this context, it is important to stress another limitation of our study, that is, the difficulty to verify with certainty the accurate occurrence of UTI and its features in a retrospective study.

The mortality rate in patients with PUVs has significantly decreased in the past decades, from 50% to less than 5% (33-35). In our study, the overall mortality was 8.1%, and there was no significant difference between antenatal (9.7%) and postnatal (7.2%) groups concerning the risk of death as well as the survival analysis. Possibly, the survival rate has improved due to multiple factors such as early diagnosis, improvement of respiratory support, and current management of renal impairment in neonates and infants. Nevertheless, in our series these advances have not apparently impacted the survival of the patients possibly due the issue of selection bias as mentioned earlier.

The decrease in mortality rate has resulted in more patients facing the long-term sequelae of PUV during puberty and adulthood, including renal function impairment and bladder dysfunction (7, 29, 36). In our series the rate of moderate to severe CKD was 37.5% (65/173) and 22.5% (39/173) patients reached end-stage renal disease. Of note, the cumulative incidence of CKD stage ≥ 3 and CKD 5 was estimated respectively

as about 56% and 31% at 18 years age. It is not a trivial task compare these data with the literature on PUV since the modern concept of CKD and its classification was established only on the beginning of 2000s (21). Before this era, there were several different classifications for so-called chronic renal insufficiency and this scenario hampers the comparison and interpretation of clinical studies in this issue. As result, the rate of progression to chronic renal insufficiency and or ESRD in patients with PUV varies widely from 22% to 68% across a number of studies (34, 37-39). Nevertheless, current series have shown renal outcome quite similar to our series. For instance, Ylinen et al.(40) have shown in a series of 46 boys that the long-term renal outcome was poor in 14 (30%) after a mean follow-up period of 12.5 years. From analysis of a large cohort with a long term follow-up of 193 patients, Heikkilä et al(7) have reported that 44 (22.8%) patients progressed to ESRD. Interestingly, Kaplan-Meier analysis estimated that the lifetime risk of ESRD in this series was 28.5%, again quite similar to our sample. Sarhan et al. (41) evaluated 120 patients with PUV using the same definitions of CKD used in our study. Follow-up time was from 2 to 16 years with a median of 3.6 years. CKD 3-5 developed at the end of follow-up in 44 patients (36.5%) and ESRD in 18 (15%).

Although the absolute risk for hypertension and proteinuria has been greater in postnatal group, this difference did not remained significant after adjustment by the survival analysis. Nevertheless, it should be pointed out the estimated high incidence of these covariables in our series. At 10 years of age, the figure was 18% and 40% for hypertension and proteinuria, respectively. Urinary tract obstruction and reflux nephropathy have been regarded as the most common disorders leading to hypertension in childhood (42, 43). In the PUV context, Parkhouse et al.(34) have shown that seven (8.7%) among 80 patients were hypertensive in an average follow-up of 5 years.

These clinical variables are well-known predictors of renal function deterioration in long-term follow-up studies with children and adults (44-48). Therefore, routine screening for hypertension with intermittent assessment of proteinuria and renal function during the entire follow-up seems to be an advisable measure in this population. Moreover, current evidence suggests that optimizing the care for the common cofactors, such as high blood pressure, proteinuria, metabolic acidosis, and anemia, may slow CKD progression and thus possibly avoid or delay the progression to ESRD (47-53).

In conclusion, after about twenty years of systematic approach to prenatally detected nephrouropathies, our understanding of clinical course of CAKUT has clearly improved. Nevertheless, it can be inferred by our analysis that, for severe kidney and urinary tract anomalies such as PUV, the renal outcome has not improved with early diagnosis and management. Unfortunately, renal failure in patients with PUV is often caused by renal dysplasia that is already established at birth because of fetal obstruction(54). Therefore, we believe that these patients possibly can benefit from the earlier diagnosis by a more strict management with the identification of modifiable cofactors such as proteinuria, blood pressure, and bladder dysfunction allowing prompt intervention in order to slow the progression of CKD. Further prospective studies and clinical trials are obviously necessary to establish the best interventions for these modified factors in children with PUV and to propose a tailored therapeutic approach.

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Conflicts of interest: none

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Table 1. Characteristics of children with PUV according to clinical presentation (n=173), Pediatric Nephrology Unit, HC/UFMG, 1970-2015

Variables	Prenatal n = 62 (%)	Postnatal n = 111 (%)	P-value
Period of admission			
1970 – 1989	3 (4.80)	47 (42.3)	<0.001
1990 - 2015	59 (95.2)	64 (57.7)	
Age of admission (months)			
Median (IQ range)	1.0 (0.5 – 4.5)	25.2 (7.6 – 43.2)	<0.001
VUR			
Absent	22 (35.5)	39 (35.1)	0.14
Unilateral	21 (33.9)	24 (21.6)	
Bilateral	19 (30.6)	48 (43.2)	
Primary surgical intervention*			
Transurethral ablation	25 (44.6)	73 (65.8)	0.029
Vesicostomy	25 (44.6)	29 (26.1)	
Other urinary diversion	6 (10.7)	9 (8.1)	
Creatinine (mg/dl)			
Median (IQ range)	0.80 (0.47 – 1.51)	0.86 (0.60 – 1.60)	0.16
GFR (ml/min/1.73m^2)			
Median (IQ range)	27.5 (13.5 – 67.1)	47.3 (21.0 – 78.3)	0.02
Nadir Creatinine (mg/dl)			
Median (IQ range)	0.52 (0.30 – 1.14)	0.61 (0.45 – 1.08)	0.07

*6 children of antenatal group died before any surgical intervention

Table 2. Clinical outcomes in children with PUV according to clinical presentation (n=173), Pediatric Nephrology Unit, HC/UFMG, 1970-2015

Variables	Antenatal n = 62 (%)	Postnatal n = 111 (%)	P-value
Urinary tract infection			
Present	42 (67.7)	106 (95.5)	<0.001
Absent	20 (32.3)	5 (4.5)	
Recurrent UTI			
Present	17 (27.4)	71 (64)	<0.001
Absent	45 (72.6)	40 (36)	
UTI episodes/year			
Median (IQ range)	0.22 (0.0 – 0.68)	0.70 (0.26 – 3.1)	<0.001
Voiding Dysfunction*			
Present	15 (41.7)	23 (29.5)	0.20
Absent	21 (58.3)	55 (70.5)	
Proteinuria			
Mean survival time	154.9	147.8	0.76
(CI95%)	(124.2 – 185.6)	(127.0 - 168.6)	
Hypertension			
Mean survival time	239.5	203.6	0.28
(CI95%)	(210.2 – 268.9)	(182.6 – 224.5)	
Chronic Kidney Disease			
Mean survival time	161.3	169.6	0.57
(CI95%)	(129.8 – 192.7)	(146.7 – 192.5)	
End-stage renal disease			
Mean survival time	213.0	223.6	0.28
(CI95%)	(179.9 – 246.2)	(203.9 – 243.3)	
Patient survival			
Mean survival time	254.1	258.5	0.31
(CI95%)	(233.0 – 275.2)	(244.8 – 272.2)	

*Missing data for 59 patients: 11 infants without sphincter control, 18 patients with urinary diversion and 30 without clinical information.

Figures

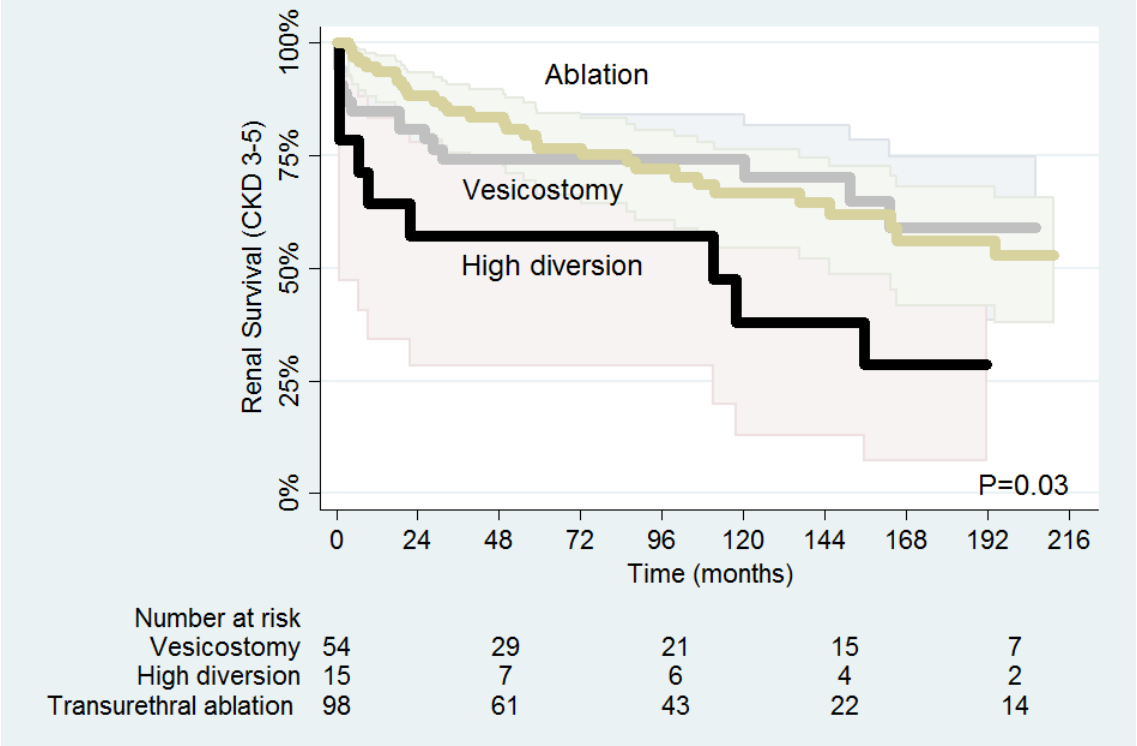

Figure 1. Kaplan-Meier curves showing the probability of CKD ≥ 3 according to primary surgical intervention. The shaded areas represent the 95% confidence intervals. Number of patients at risk is shown below x-axis, Pediatric Nephrology Unit, HC/UFMG, 1970-2015.

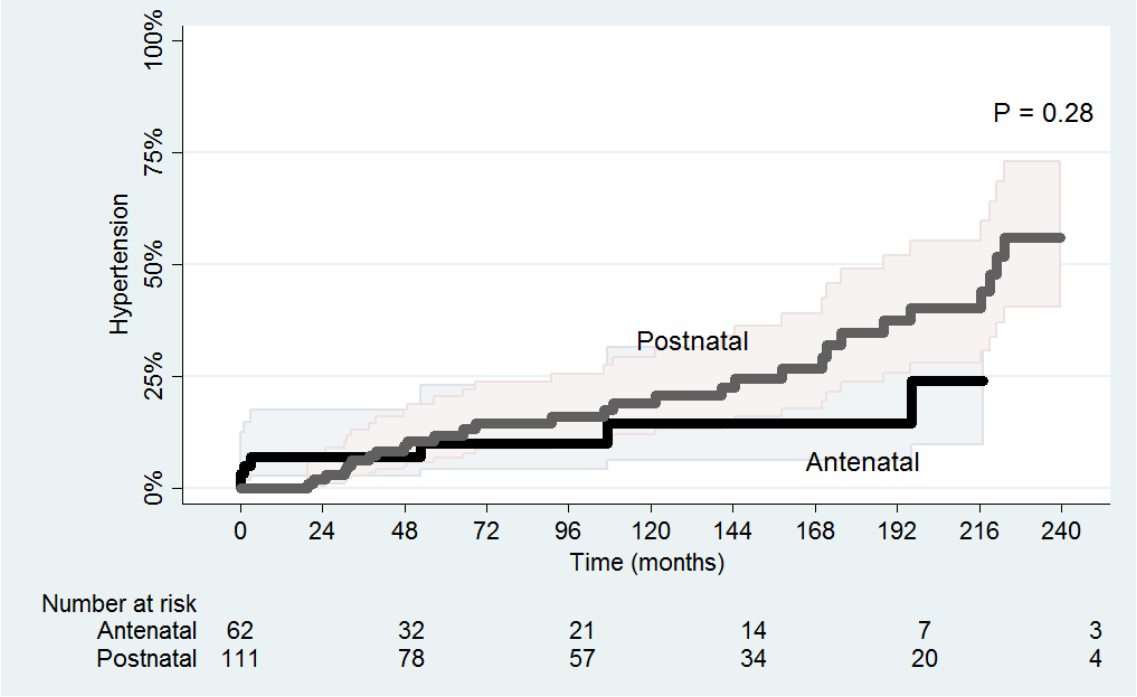

Figure 2. Kaplan-Meier survival curves reveal cumulative incidence of hypertension according to clinical presentation. The shaded areas represent the 95% confidence intervals. Number of patients at risk is shown below x-axis, Pediatric Nephrology Unit, HC/UFMG, 1970-2015

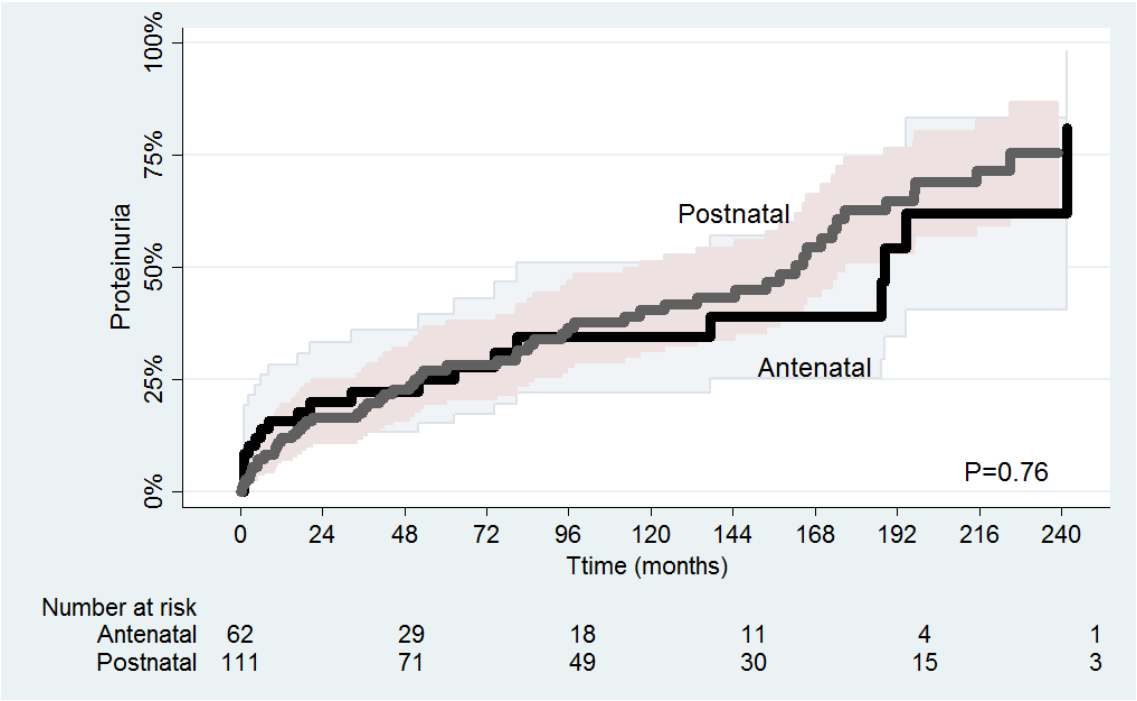

Figure 3. Kaplan-Meier survival curves reveal cumulative incidence of proteinuria according to clinical presentation. The shaded areas represent the 95% confidence intervals. Number of patients at risk is shown below x-axis, Pediatric Nephrology Unit, HC/UFMG, 1970-2015.

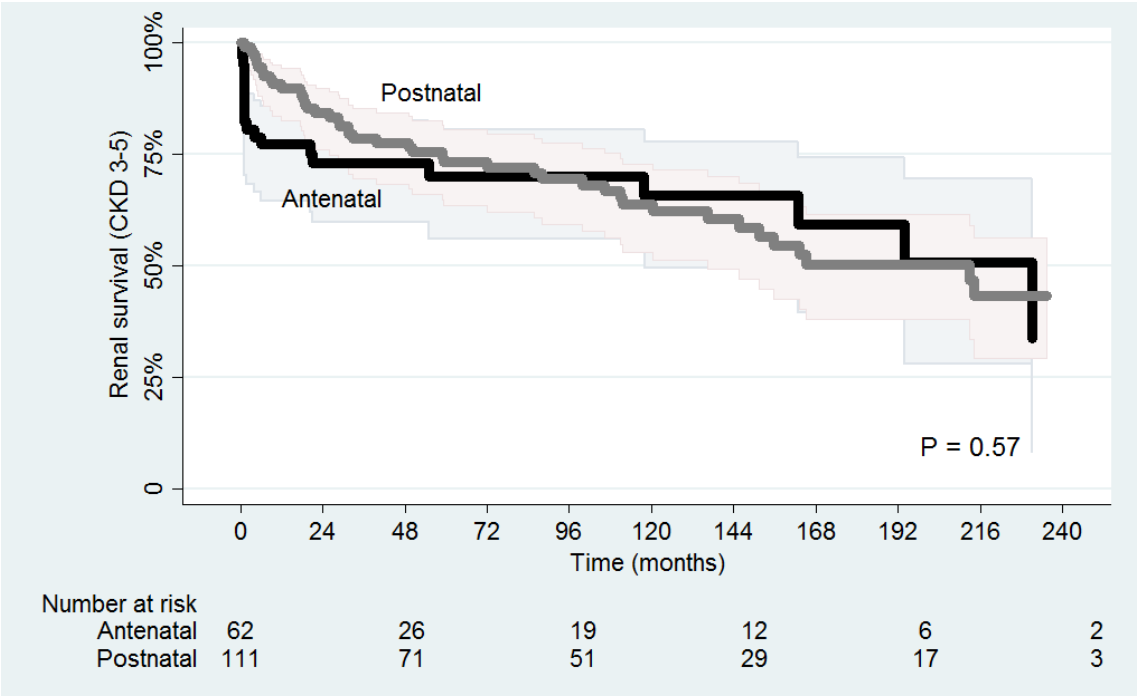

Figure 4. Kaplan-Meier curves showing the probability of CKD ≥3 according to clinical presentation. The shaded areas represent the 95% confidence intervals. Number of patients at risk is shown below x-axis, Pediatric Nephrology Unit, HC/UFMG, 1970-2015.

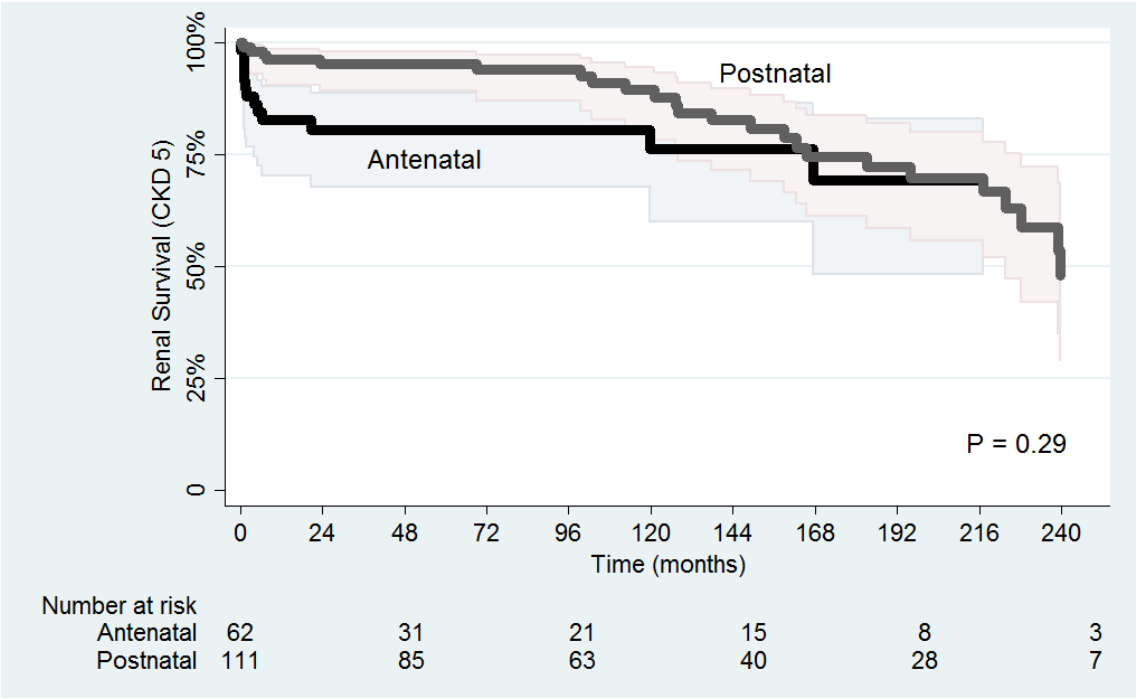

Figure 5. Kaplan-Meier curves showing the probability of CKD 5 according to clinical presentation. The shaded areas represent the 95% confidence intervals. Number of patients at risk is shown below x-axis, Pediatric Nephrology Unit, HC/UFMG, 1970-2015.

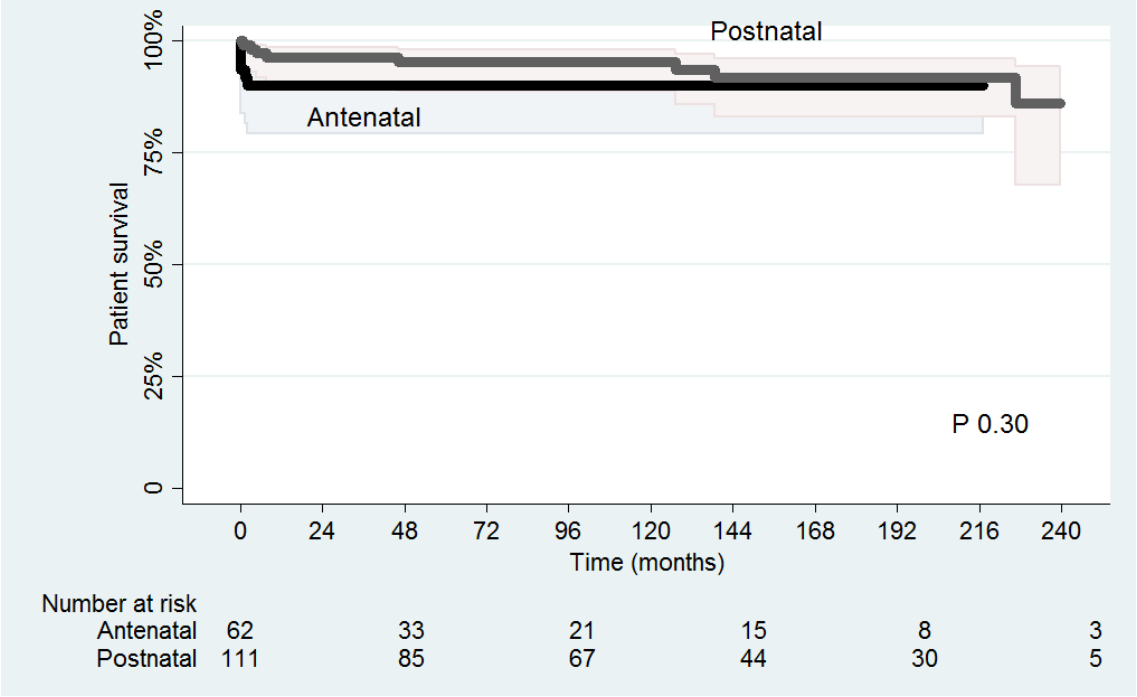

Figure 6. Kaplan-Meier curves showing the probability of death according to clinical presentation. The shaded areas represent the 95% confidence intervals. Number of patients at risk is shown below x-axis, Pediatric Nephrology Unit, HC/UFMG, 1970-2015.

9. ANEXOS

ANEXO A

UFMG

Universidade Federal de Minas Gerais
Comitê de Ética em Pesquisa da UFMG - COEP

Parecer nº. ETIC 109/07

Interessado(a): Prof. Eduardo Araújo Oliveira
Depto. Pediatria
Fac. Medicina -UFMG

DECISÃO

O Comitê de Ética em Pesquisa da UFMG – COEP aprovou, no dia 15 de maio de 2007,após atendidas as solicitações de diligência, o projeto de pesquisa intitulado **"Anomalias congênitas do trato urinário: do diagnóstico pré-natal à prevenção da doença renal crônica"** bem como o Termo de Consentimento Livre e Esclarecido.

O relatório final ou parcial deverá ser encaminhado ao COEP um ano após o início do projeto.

Profa. Dra. Mariza Santos Castro
Vice -Presidente do COEP-UFMG
Presidente em Exercício

Av. Pres. Antonio Carlos, 6627 – Unidade Administrativa II - 2º andar – Sala 2005 – Cep31270-901 – BH-MG
Telefone: (031) 3499-4592- FAX: (031)3499-4516 - e-mail: prpq@coep.ufmg.br

ANEXO B

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

TITULO DO PROJETO:

Anomalias congênitas do trato urinário: do diagnóstico pré-natal à prevenção da doença renal crônica

Por meio deste termo de consentimento, informamos que estamos desenvolvendo uma pesquisa no Hospital das Clínicas da UFMG para estudarmos os problemas que aparecem durante a gravidez nos rins de algumas crianças. Esses problemas podem ser diagnosticados durante a gravidez por ultrassonografia, e caso não sejam diagnosticadas e tratados após o nascimento podem ocasionar pressão alta e perda da função dos rins. Este estudo quer saber se essas doenças têm causa genética, familiar e se o diagnóstico e o tratamento apropriados podem proteger as crianças desses graves problemas.

Os exames para os estudos genéticos serão coletados através de punção venosa, aproveitando a mesma coleta dos outros exames de rotina do paciente. Estamos garantindo que a realização dos exames somente será autorizada após assinatura deste termo de consentimento por um responsável pelo paciente. Garantimos ainda que a identidade e a privacidade do paciente serão mantidas. Os resultados desse estudo somente serão utilizados para aumentar os conhecimentos da medicina. Os dados desse estudo têm também como finalidade serem utilizados em teses de doutorado.

Finalmente, será resguardado o direito de recusa em participar do trabalho em qualquer etapa do mesmo, sabendo-se que o paciente continuará a receber o tratamento convencional das doenças renais, tendo assim garantida sua assistência médica.

Eu, _____, mãe, (ou pai ou responsável) pelo paciente_____entendi tudo que foi explicado sobre a pesquisa e concordo que meu filho (ou minha filha ou outro grau de parentesco) participar das coletas de sangue e urina para o estudo das doenças renais.

Este estudo será feito pelos doutores: Débora Marques Miranda, Ana Cristina Simões e Silva, Eduardo Araújo Oliveira, e Maria Cândida Bouzada Viana do Hospital das

Clínicas da UFMG (TELEFONE: 32489445). Dou meu consentimento para que seja coletado sangue e urina de meu filho (minha filha ou outro grau de parentesco) para estudar se as doenças dos rins que aparecem no ultrassom durante a gravidez têm tendência familiar. Confirmo que meu filho (minha filha ou outro grau de parentesco) foi selecionado de forma voluntária para participar dessa pesquisa. Entendo ainda que os resultados do estudo serão entregues aos responsáveis pelos pacientes. Eu assinei e recebi uma cópia dessa autorização.

Data e local:_____

Assinatura
do responsável:_____

Grau de parentesco
do responsável:_____

Assinatura
do pesquisador:_____

Eduardo Araújo Oliveira

Endereço: Av. Alfredo Balena, 190 – Faculdade de Medicina – Departamento de Pediatria Fone: 32489445

EM CASO DE DÚVIDA, entre em contato com:
COEP/UFMG: Conselho de Ética em Pesquisa da UFMG: Av. Antônio Carlos, 6627- Unidade Administrativa II – segundo andar - Fone: 3499 4592

ANEXO C

UNIVERSIDADE FEDERAL DE MINAS GERAIS

PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA SAÚDE
SAÚDE DA CRIANÇA E DO ADOLESCENTE

UFMG

FOLHA DE APROVAÇÃO

MODELOS DE PREDIÇÃO EM ANOMALIAS CONGÊNITAS DO TRATO URINÁRIO: NECESSIDADE DE CIRURGIA E PROGRESSÃO PARA DOENÇA RENAL CRÔNICA

MARIANA AFFONSO VASCONCELOS

Tese submetida à Banca Examinadora designada pelo Colegiado do Programa de Pós-Graduação em Ciências da Saúde, Saúde da Criança e do Adolescente, como requisito para obtenção do grau de Doutor em Ciências da Saúde, Saúde da Criança e do Adolescente, área de concentração Ciências da Saúde.

Aprovada em 15 de setembro de 2016, pela banca constituída pelos membros:

Prof.ª Ana Cristina Simões e Silva - Coorientadora
UFMG

Prof. José Maria Penido Silva
UFMG

Prof. Enrico Antônio Colosimo
UFMG

Prof.ª Vera Maria Santoro Belangero
UNICAMP

Dr.ª Cristina Maria Bouissou Morais Soares
UFMG

Belo Horizonte, 15 de setembro de 2016.

ANEXO D

UNIVERSIDADE FEDERAL DE MINAS GERAIS

PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA SAÚDE
SAÚDE DA CRIANÇA E DO ADOLESCENTE

UFMG

ATA DA DEFESA DE TESE DA ALUNA
MARIANA AFFONSO VASCONCELOS

Realizou-se, no dia 15 de setembro de 2016, às 09:00 horas, na sala 62, andar térreo da Faculdade de Medicina, da Universidade Federal de Minas Gerais, a defesa de tese, intitulada **"MODELOS DE PREDIÇÃO EM ANOMALIAS CONGÊNITAS DO TRATO URINÁRIO: NECESSIDADE DE CIRURGIA E PROGRESSÃO PARA DOENÇA RENAL CRÔNICA"**, apresentada por **MARIANA AFFONSO VASCONCELOS**, número de registro 2013670162, graduada no curso de MEDICINA, como requisito parcial para a obtenção do grau de Doutor em Ciências da Saúde, pelo Programa de Pós Graduação em Ciências da Saúde, Saúde da Criança e do Adolescente, à seguinte Comissão Examinadora formada pelos Professores Doutores:. Ana Cristina Simões e Silva - Coorientadora (UFMG), José Maria Penido Silva (UFMG), Enrico Antônio Colosimo (UFMG), Vera Maria Santoro Belangero (UNICAMP), Cristina Maria Bouissou Morais Soares (UFMG).

A Comissão considerou a tese:

(X) Aprovada

( ) Reprovada

Finalizados os trabalhos, lavrei a presente ata que, lida e aprovada, vai assinada por mim e pelos membros da Comissão.
Belo Horizonte, 15 de setembro de 2016.

Prof.ª Ana Cristina Simões e Silva (Doutora)

Prof. José Maria Penido Silva (Doutor)

Prof. Enrico Antônio Colosimo (Doutor)

Prof.ª Vera Maria Santoro Belangero (Doutora)

Dr.ª Cristina Maria Bouissou Morais Soares (Doutora)

Centro de Pós Graduação
Faculdade de Medicina-UFMG
Av. Prof.Alfredo Balena , 190- 5º Andar
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