ALMA MATER STUDIORUM

UNIVERSITÀ DI BOLOGNA

PROFESSIONAL MASTER'S PROGRAMME 2ND LEVEL

MASTER IN PEDIATRIC UROLOGY: CONTEMPORARY STRATEGIES FROM FETAL LIFE TO ADOLESCENCE

Thesis:

How often correlates a prenatal diagnosed urinary tract dilatations (UTD) with a perinatal cut off 7-10mm pyelon dilatation to postnatal developement of CAKUT (congenital anomalies of kidney and urinary tract)?

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Index of Content

1. Introduction

1.1. Problem

Urinary tract dilatation (UTD) is a common problem at prenatal ultrasound. It occurs 1-2% in all pregnancies. In Switzerland are noted 870-1750/y.

The majority of the neonatal cases 50-70% UTD is transient or physiologic and there are no clinical consequences reported.
In other cases a relevant problem postnatal with further investigations and anatomical pathologies like UPJO (Ureteropelvicjunction Obstruction), Megaureter, VUR (Vesicoureteral Reflux), Duplexsystems or PUV (posterior urethral valve) are found.

Parents are concerned about abnomal findings at the prenatal ultrasound and want to know about the risks or prognostic factors of outcome.
Furthermore with the introduction of ultrasound screening programs during the last years the detection of more patients with mild hydronephrosis was possible.

It is an important job of clinicians to filter these patients who could develop problems of CAKUT (Congenital Anomalies of Kidney and Urinary Tract).
Several predicting factors are discussed. For sure Oligohydramnios, renal cysts, bladder outlet obstruction, further organic malformations and and prematurity are negative prognostic factors (1).

Cordero et al (2) found out that the prenatal consultation of a pediatric urologists has an positive impact to the postnatal outcome, more than the geographical infrastructure and proximity to pediatric urologists or the severity of prenatal hydronephrosis.

We know that interdisciplinary work (gynecologist, pediatrician, nephrologist and pedatric urologist) is important to bring together prenatal and postnatal datas and patients leading. But there is still a lack of correlation between prenatal UTD and postnatal uropathological findings like CAKUT concerning to intersdisciplinary co-working, terminology, infrastructure and patientleading.

Evaluating the relevant patients after birth takes a lot of time and costs to find out the clinically significants uropathies. Alternatively not to evaluate any child with UTD might lead to delay of diagnosis of significant uropathies and irreversible loss of renal function. Therefore, the definition of a cut-off is important for the joint diagnosis of interdisciplinary medical groups.

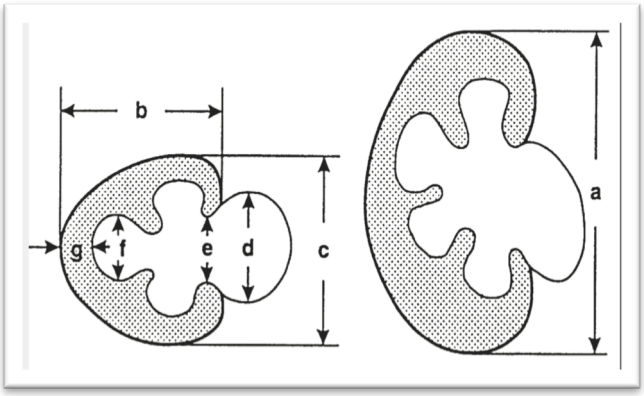
In our hospital prenatal UTD are discussed prenatal at an interdisciplinary board and are referred after birth to our center of children hospital (Department Ped. Urology or Nephrology).
Furthermore we receive many other referrals from gynecologists (practitioner), peripheral birth clinics or pediatricians (incl. incidental findings at the 4weeks hip ultrasound*)*

We asked ourselves what percentage of children we overdiagnose with pre- and perinatal measured pyelon dilatation 7-10mm and >10mm. In this study, we focused on the measurements with 7-10 mm of pyelon dilatation.

1.2. Backround

Terminology and Definition
Generally there was for a long episode no uniform classification how to define an UTD between the prenatal and postnatal episode.

Several different terminology are used for example a “mild hydronephrosis” is described as an urinary tract dilatation of the pyelon but you know nothing about other factors like parenchymal thickness or appearance and nothing about der ureter and a possible distal obstruction like PUV. The PUV has another outcome than a mild isolated UTD.



Radiological measurements:

a) Maximal longitudinal diameter kidney
b) Transverse Diameter Kidney
c) Anterior-Posterior Diameter Kidney
d) Anterior-Posterior Diameter Hilus (extrarenal)
e) Anterior-Posterior Diameter Hilus (intrarenal, cortex level)
f) Maximal Dilatation of Calices
g) Minimal Thickness of renal Cortex

Abbildung 1

Diagnostik bei konnatalen Dilatationen der Harnwege (APN Konsensusgruppe, Betz et al; Urologe A, 2001

Different grading systens are utilized like descriptive APD (AnteriorPosteriorDiameter) Classifications (e.g. mild-moderate-severe) or quantitative systems (e.g. measurement of the anterior-posterior renal pelvic diameter (APRPD) or semi-quantitative systems like (e.g. SFU). They are used from different disciplines and some are preferred as a grading systems preferentially in prenatal evaluation while others are preferred for postnatal evaluation.

Onen et al have modified part of the various classifications in a paper 2020.
(see Illustration, Kap.7)

The APD System based on the anterior-posterior diameter of the pelvis

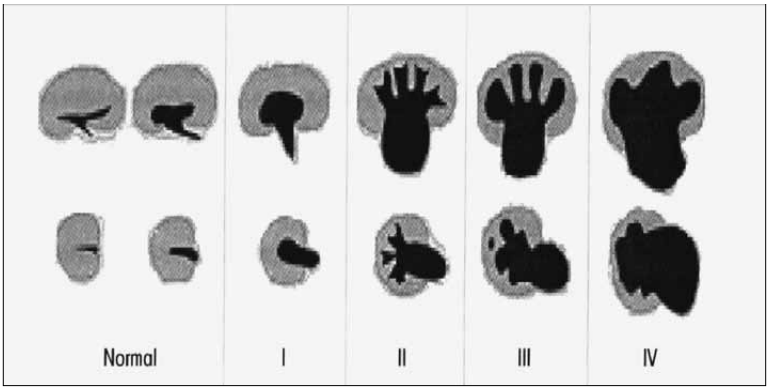
APD Grading System	
Grade	Time window/APD (mm)
Mild	Second trimester: 4 < APD < 7 Third trimester: 7 < APD < 9
Moderate	Second trimester: 7 < APD < 10 Third trimester: 9 < APD < 15
Severe	Second trimester: APD > 10 Third trimester: APD > 15

Abbildung 2

Ultrasound evaluation for prediction of outcomes and surgical decision in fetal hydronephrosis
D. Zhang, Exp. and therapeutic Medicine; 2019

The measurement of the AP diameter alone can vary greatly depending on the child's hydration status and bladder emptying. There is no description of the parenchyma in this classification

SFU Classification



A, SFU grading system

Grade	Characteristics
0	No hydronephrosis
I	Renal pelvis is slightly separated
II	Renal pelvis is further separated and a single or a few dilated calices may be visualized
III	All calices are dilated
IV	All calices are dilated and the renal parenchyma over the calices is thinned

Abbildung 3

SK. Fernbach. Ultrasound grading of hydronephrosis: introduction to the system used by the Society for Fetal Urology. Pediatr Radiol 1993

There are a few disadvantages in the SFU grading. For example the intrarenal pelvic caliceal dilatation is measured without relation to the kidney size and the APRPD is not directly measured. The SFU grading and the assessment of calices dilatation is very examiner dependent, parenchymal changes from grade II to grade III are not recorded and within grade IV it is not possible to assess whether or not there is an indication for surgery due to the severity. The wide definition of SFU Grad IV makes prognosis difficult to predict for example a relevant UPJO

Although the literature has shown that this classification is the most commonly used and has the best consistency (4).

Mostly the UTD can be documented up to the 16th week of gestational age (normal values <4mm) and further on in the second trimester up to the 28th week (normal value <7mm). Postnatal the American guidelines present normal values <10mm in Europe are different postnatal management utilize for the 7-10mm postnatal APRPD.

Abbildung 4 : Normal values for Urinary Tract Dilatation Classifiction System

Ultrasound findings	Time at presentation		
	16–27 weeks	≥28 weeks	Postnatal (>48 h)
Anterior-Posterior Renal Pelvis Diameter (APRPD)	<4 mm	<7 mm	<10 mm
Calyceal dilation			
Central	No	No	No
Peripheral	No	No	No
Parenchymal thickness	Normal	Normal	Normal
Parenchymal appearance	Normal	Normal	Normal
Ureter (s)	Normal	Normal	Normal
Bladder	Normal	Normal	Normal
Unexplained oligohydramnios	No	No	NA

Nuygen, Multdisciplinary consensus on the classification of prenatal and postnatal urinary tract dilatation, JPedUrology 2014

Usually in normal fetus there is no calyceal dilation seen, the renal parenchyma appeared normal in point of thickness and structure and the ureter is not seen. The bladder is normal filled and there is no unexplained oligohydramnios.

Further sonographic parameters (Abb. 5) are important to get an overall impression of the UT dilatation and to be able to estimate the prognostic development.

Abbildung 5: US parameters included int the Urinary Tract Dilatation Classiication System

US parameters		Measurement/findings	Note
Anterior-Posterior Renal Pelvic Diameter (APRPD)		(mm)	Measured on transverse image at the maximal diameter of intrarenal pelvis
Calyceal dilation	Central (major calyces) Peripheral (minor calyces)	Yes/No Yes/No	
Parenchymal thickness		Normal/Abnormal	Subjective assessment
Parenchymal appearance		Normal/Abnormal	Evaluate echogenicity, corticomedullary differentiation, and for cortical cysts
Ureter		Normal/Abnormal	Dilation of ureter is considered abnormal; however, transient visualization of the ureter is considered normal postnatally
Bladder		Normal/Abnormal	Evaluate wall thickness, for the presence of ureterocele, and for a dilated posterior urethra

Nuygen, Multdisciplinary consensus on the classification of prenatal and postnatal urinary tract dilatation, JPedUrology 2014

In 2014 Nguyen has published the interdisciplinary consensus of a conference with eight societies ((American College of Radiology (ACR), the American Institute of Ultrasound in Medicine (AIUM), the American Society of Pediatric Nephrology (ASPN), the Society for Fetal Urology (SFU), the Society for Maternal-Fetal Medicine (SMFM), the Society for Pediatric Urology (SPU), the Soci- ety for Pediatric Radiology (SPR) and the Society of Radiologists in Ultrasounds (SRU)).
They developed an unified grading system (UTD-P1-P3) for perinatal UT dilation.
In this grading all significant abnormal urinary findings beside of UT are combined together including the kidney, ureter, and bladder.

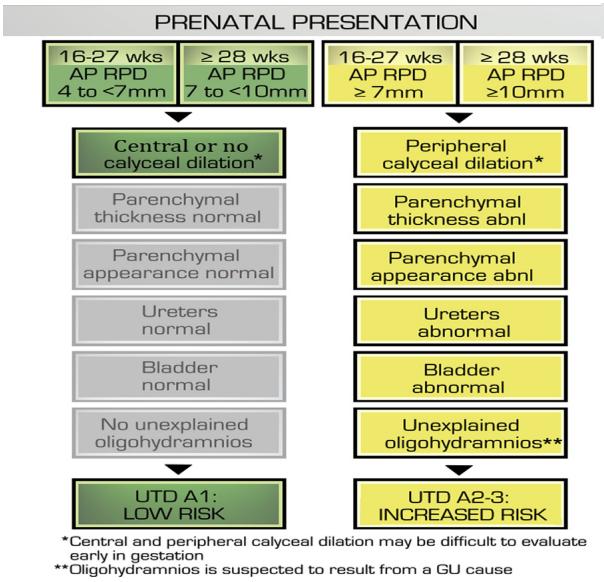


Abbildung 6

Urinary Tract Dilation (UTD) Risk Stratification - Prenatal Presentation for UTD A1 (low risk) and UTD A2e3 (increased risk). Note: Classification is based on the presence of the most concerning feature. For example, a fetus with an anterior-posterior renal pelvis diameter (ARPRD) within the UTD A1 range but with peripheral calyceal dilation would be classified as UTD A2e3 (as illustrated in Fig. 5C and D).

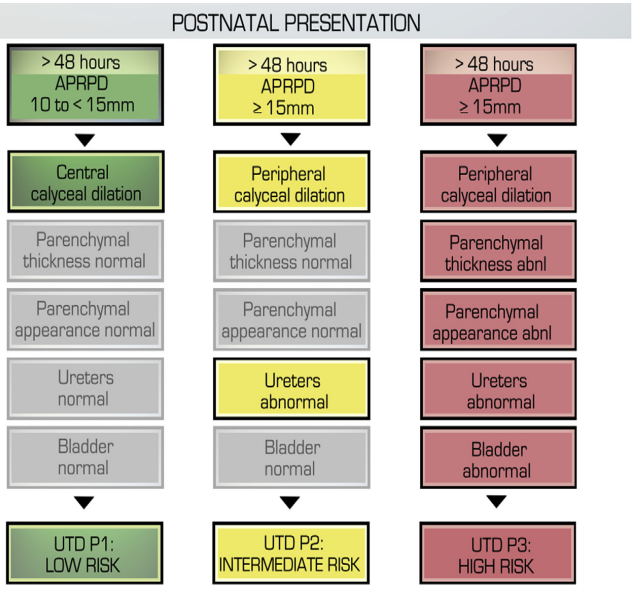


Abbildung 7

Urinary Tract Dilation (UTD) Risk Stratification e Postnatal Presentation for UTD P1 (low risk), UTD P2 (intermediate risk), and UTD P3 (high risk). Note: Stratification is based on the most concerning ultrasound finding. For example, if the anterior- posterior renal pelvis diameter (APRPD) is in the UTD P1 range, but there is peripheral calyceal dilation, the

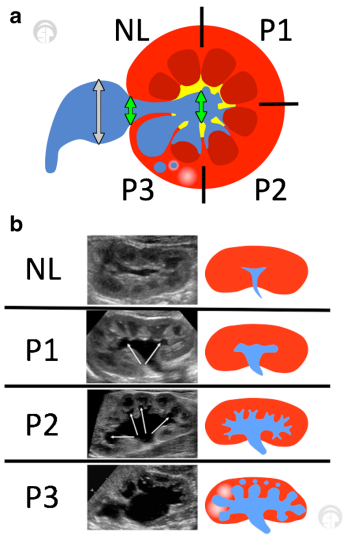


Abbildung 8 UTD-(P1-P3) Classification

Chow, Classification of pediatric urinary tract dilation: the new language, Pediatr Radiol (2017)

Based on this classification they recommend and management schema for prenatal and postnatal period.

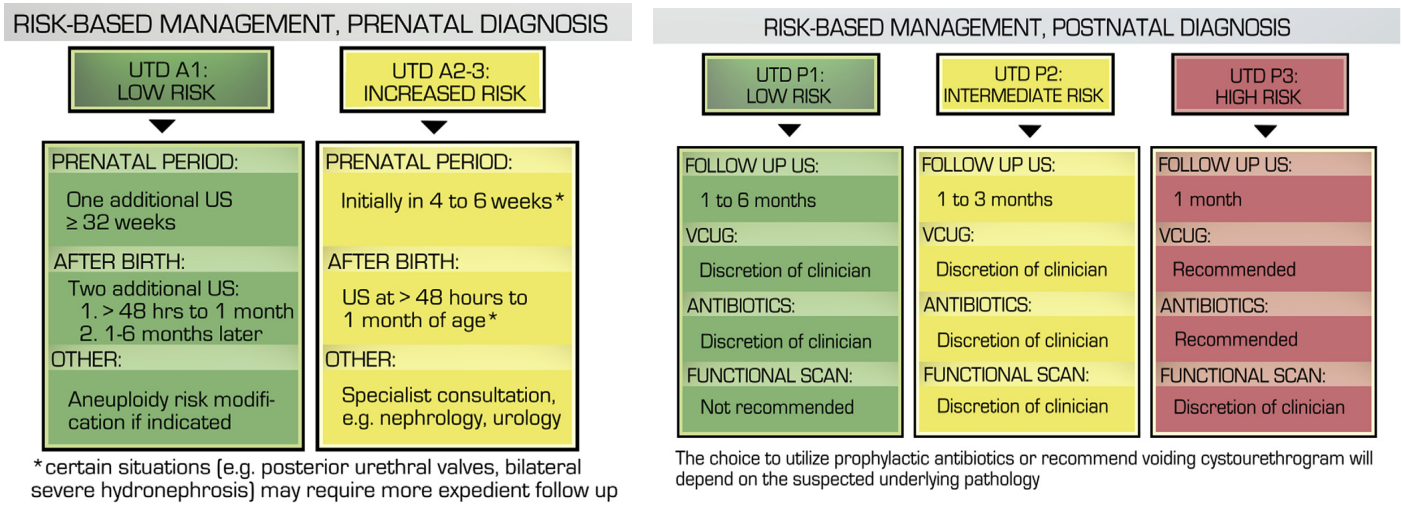


Abbildung 9

Nguyen et al, Multidisciplinary consensus on the classification of prenatal and postnatal urinary tract dilation (UTD classification system), Journal of Ped. Urology (2014)

They wanted to propose a standardised scheme based on sonographic criteria that also maps the change in timing from prenatal to postnatal changes.

It is not based on evidence thats why it has to be validated and modified with the clinical experiences. Criticisms remain: there is no good differentiation of peripheral and central calices within UTD-P1-P2 and within UTD-P3 there is no indication of severity, which cases have a poor prognosis and e.g. lead to direct surgery and others can be further controlled.

Therefore the need and discussion for an single grading system that can be use in prenatal and postnatal episodes to describe UT dilatation is ongoing .

1.3. Pathologies

The causes of infantile UTD range from potentially diagnoses that always require therapy, such as urethral valves or often relevant ureteropelvic obstruction to harmless idiopathic and transient UTD.

Often other related malformations are found, so we subsumed these under the term CAKUT.
According to the 2006 annual report of the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) renal pelvic dilatation due to obstruction is the leading cause of chronic renal failure in children, accounting for an estimated 22 % (5). According

to this report, obstructive kidney disease is also responsible for 15.9% of kidney transplantations in children.

That's why it is important to identify a transient or relevant pathology as early as possible.

Etiology of urinary tract dilatation detected by prenatal ultrasound

Etiology	Incidence (%)
Transient/physiologic	50–70
Ureteropelvic junction obstruction	10–30
Vesicoureteral reflux	10–40
Ureterovesical junction obstruction/megaureter	5–15
Multicystic dysplastic kidney disease	2–5
Posterior urethral valves	1–5
Ureterocele, ectopic ureter, duplex system, urethral atresia, Prune belly syndrome, polycystic kidney diseases, l cysts	Uncommon

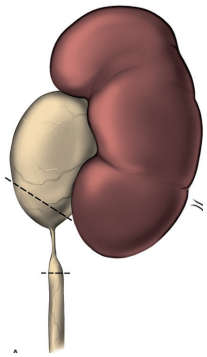
Abbildung 10 Nguyen 2014

Nguyen et al, Multidisciplinary consensus on the classification of prenatal and postnatal urinary tract dilation (UTD classification system), Journal of Ped. Urology (2014) 18, 982-999

Transient UTD

This is the largest group with 50-70% of the prenatal often mild to moderately pronounced UTD. The degree of the UTD often decrease even during the pregnancy or during the first year of life.
Transient dilatation of the renal pelvic caliceal system is probably due to immaturity of the smooth muscles and the presence of ureteral folds which obstruct the flow of urine in the newborn. This phenomenon disappears spontaneously during the first 6 weeks of life.

Uretero-Pelvic Junction Obstruction



UPJO occurs in 5–20% of children with antenatally diagnosed renal pelvis dilation and is caused by intrinsic stenosis/valves, peripelvic fibrosis or an crossing vessels at the level of junction between the pelvis and the ureter.
UPJO is usually unilateral (left > right), more common in boys and in the vast majority of cases primarily congenital. Only very rarely is there a secondary cause (like tumor, infection, urolithiasis, postoperatively).

It is suspected on the observation at US of a dilated renal pelvis (often >15 mm) and dilated calyces in the absence of any dilatation of ureter or bladder.

The postnatal management of children with antenatally detected UPJO remains several diagnostic pathways. The essential question is whether the child should be operated or managed conservatively.
In many cases, this requires a functional diagnostic with an outflow determination (either by MAG-3 scintigraphy or functional MRU).

In case of relevant outflow obstruction and reduced function (<40-42%), surgery is indicated in most cases.
If the findings are doubtful, a follow-up examination is initiated and if there is a relevant deteriorating split renal function or delayed cortical transit, surgery is also indicated.

VUR (Vesicoureteral Reflux)

VUR is the retrograde flow of urine from the bladder upward to the upper urinary tract.
The grading system for VUR includes grade I to V which correspond to increasingly severe VUR.

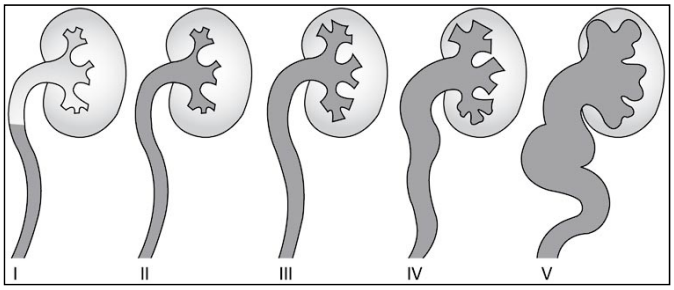


Abbildung 11 International Classication of vesicoureteral reflux (Nature, Clinical Practice Nephrology 2007)

The closure mechanisms of the uretero-vesical junction are normally guaranteed by:

- The length of the submucosal course and its relationship to the calibre of the ureter.
- The strength of the posterior muscular support of the ureter.
- The strength of the anchorage and localisation in the trigonum
- The integrity of the terminal ureter

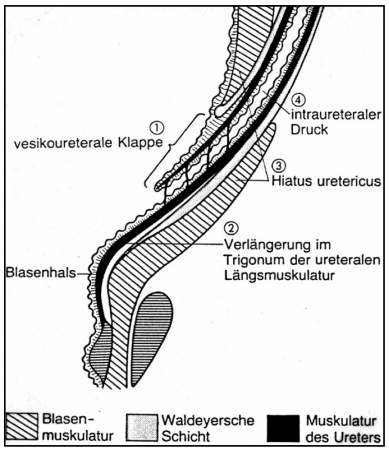


Abbildung 12 Ureterovesical orifice (from Bettex 1975

Primary VUR is the result of a congenital malformation of these closure mechanisms. It is assumed that this system matures during growth, which explains the frequent spontaneous healing of VUR.
Secondary VUR is the result of an underlying condition such as a mechanical obstruction (e.g. urethral valves) or a functional obstruction (e.g. neurogenic bladder, detrusor-sphincter dyscoordination). Refluxive UTD are often less pronounced prenatal compared to obstructive UTD and are more difficult to predict with varying volume in the ureter.

Although it is more difficult to diagnose neonatal VUR, it is important to assess the risk of pyelonephritis and renal scarring later in life, which can lead to hypertension and ESRD (end-stage renal disease).

Uretervesical junction obstruction/ Megaureter

Megaureters are defined as dilatations of the ureter ≥ seven millimetres postnatal.
The primary Megaureter is often due to an anatomical or functional obstacle, usually as a congenital malformation in the area of the distal ureteral segment.
More rarely, megaureter is the result of an increase in bladder pressure with a neurogenic bladder or posterior urethral valves. This is called secondary megaureter.

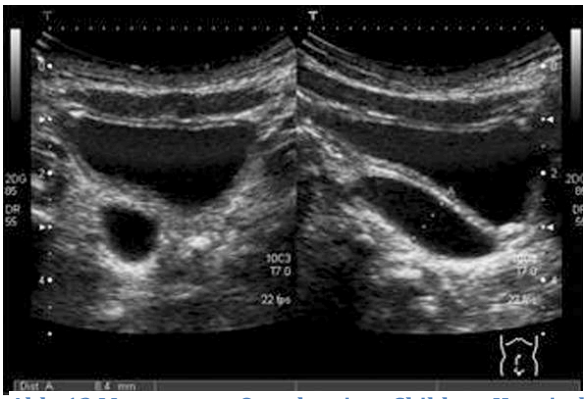


Abb. 13 Megaureter, Ostschweizer Children Hospital

This clinical entity within congenital hydronephrosis is a relatively small group, but represents a significant patient group due to the increased risk of urinary tract infections in the first year of life. For these children further clarification to exclude VUR by means of a VCUG is indicated.

The diagnosis is made by ultrasound, the degree of obstruction can be evaluated by dynamic renal scintigraphy (e.g. using MAG-3 Scintigraphy).

The presence of vesicoureteral reflux or obstruction determines the further therapeutic approach. The necessity of antibiotic prophylaxis in megaureter is discussed.
Non-obstructive, non-refluxive megaureter does not require surgical intervention; it is controlled by ultrasound.
Long-term antibiotic prophylaxis and/or circumcision has to be discussed to boys in the first year of life to prevent urinary tract infections. The spontaneous maturation tendency of megaureters is high in the first years (1-3y) of life.
Surgical intervention is indicated in the presence of symptoms as recurrent febrile UTIs, occurence of Urolithiasis, impaired renal function associated with massive or progressive hydronephrosis or a drop in differential function on serial renograms. In these cases it is recommended to do a ureteral reimplantation in patients over 1 year of age even though the procedure may be challenging and the outcome worse compared to other operations.

Ureteroceles are special forms that also lead to ureteral dilatation. These are usually associated with duplex systems and affect the upper part of the corresponding duplex system. Ureteroceles are frequently diagnosed prenatally and after appropriate clarification usually treated minimally invasively in the first months of life by means of endoscopic incision of the ureterocele.

PUV (posterior urethral valve)

Posterior urethral valves are among the most severe obstructive uropathies.

The urethral valves are mucosal folds distal to the colliculus seminalis which are a drainage obstruction that affects the entire urinary tract and can have dramatic consequences on renal function.

The affected children often present prenatally at a very early stage (in some cases in the first trimester up to the 16th week of gestation).

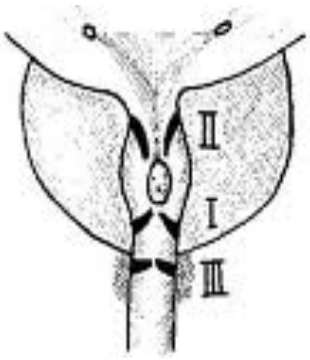


Abbildung 14 Classification Urethral Valv (Young)

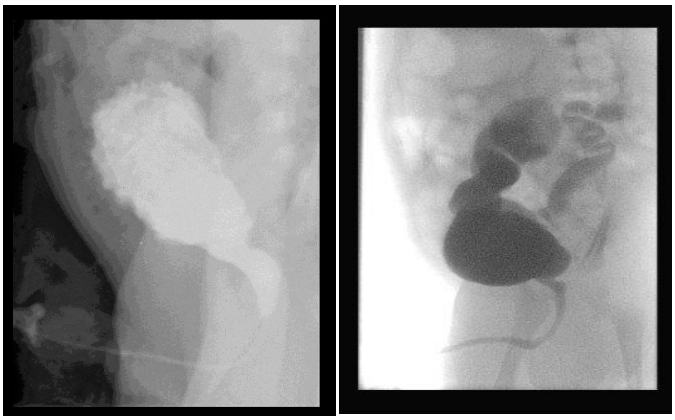


Abbildung 15 VCUG of 2 Patients with PUV ; Ostschweizer Children Hospital

Depending on the severity, an oligohydramnios accompanied by a megacystis with a thickened bladder wall and bilateral, pronounced UTD is found prenatally. In addition to the megacystis, there is a dilated prostatic urethra ("pear-shaped" posterior urethra) and a thickened bladder wall with bilateral vesicorenal reflux. Prepartum ultrasound typically shows a dilated prostatic urethra as a "keyhole sign". The clarification of the newborn is done by ultrasound and VCUG. In the few cases of a severe obstruction, a vesicostomy or ureterostomy must be performed; in most cases, a transurethral bladder catheter is sufficient. In the course a cystoscopic valve resection is performed if the baby is stable and over 2-3kg. Fluid and electrolyte replacement may be necessary in cases of secondary polyuria after removal of the outflow obstruction, as well as substitution with bicarbonate.

A multi-disciplinary team (paediatric urologists, nephrologists and nursing) must control the patients in short and long term follow up because we know PUV is less predictable and endstage renal failure affects 15 to 30% of children after birth (6)

If necessary various prenatal therapeutical options might be discussed according to the severity of presentation: in utero therapy, follow-up with planned post-natal management or termination of pregnancy.nFor decades several treatments have been tried: open surgical technique of fetal vesicostomy, direct endoscopic valves resection and vesicoamniotic shunting. All techniques have a poor outcome, increased mortality for mother and fetus and the improvement of longterm ESRD (endstage renal disease) is questionably proven.

In the diagnosis of lower urinary tract obstruction oligohydramnios, renal cortical

abnormalities, and early gestational age at diagnosis (e.g. <24 weeks) were found to be independent predictors of poor postnatal renal function (7).

Multicystic dysplastic kidneys and congenital kidney hypoplasia or kidney dysplasia are to be distinguished from the above pathologies. The last point is often difficult to distinguish, as dysplasia often accompanies or is a consequence of CAKUT.

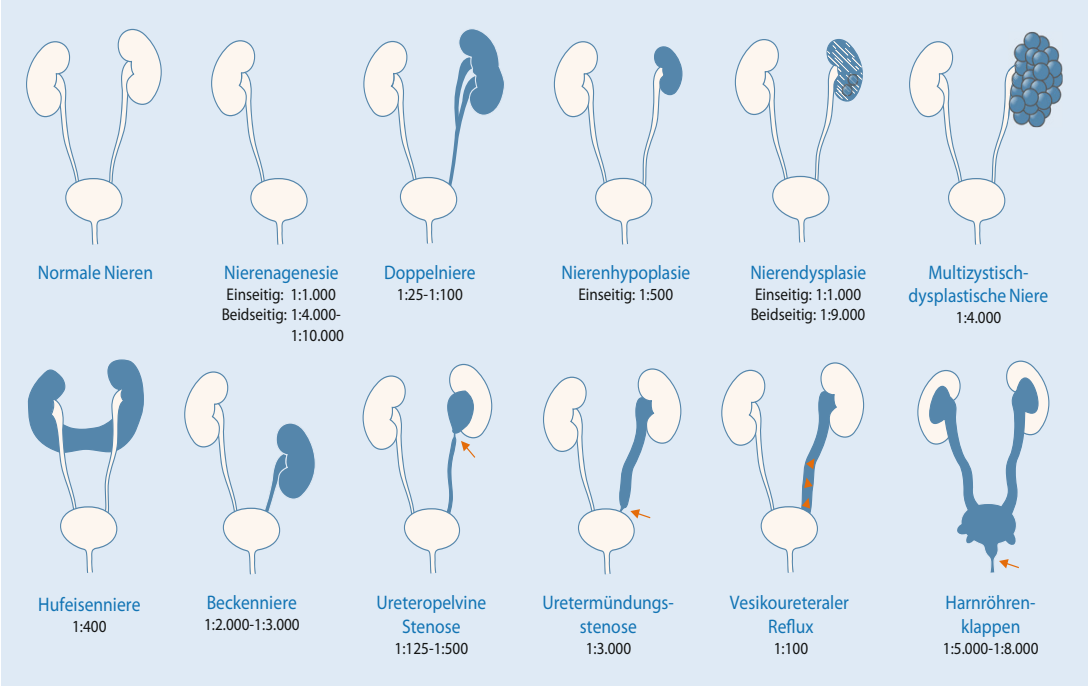


Abbildung 16

Kongenitale Anomalien der Nieren und ableitenden Harnwege (CAKUT), Kosfeld, Med. Genetik 2018

In terms of genetical research we know meanwhile that CAKUT are genetically highly heterogeneous. CAKUT occur sporadically in around 85% of patients, whereas around 15% of cases are family- related. The inheritance pattern is frequently dominant, but it can also be recessive. In mouse models 180 CAKUT- associated genes have been described. It is of clinical significance to resolve the genetic causes of CAKUT to predict the risk of recurrence and to guide evaluation of CAKUT patients with regard to extrarenal phenotypes.

2. Main Objects

2.1. Questions and Hypothesis

To refer the mentioned problems above we wanted to find out if our diagnostic pathway reflected the relevant patients who develop a CAKUT.

We want to know if our datas (last 12 years) are comparable to literature datas.

We wanted to evaluate if we decide with assumed AP Diameter prenatal >7mm as a valide cutt off in the 3rd trimenon?

How many of these patients with the cut off > 7mm develop postnatal any pathological findings?

Do we find out with a cut off post/perinatal >10mm the same critical patients and how many of those develop pathological findings?

Are there any other risk factors we can clarify with our datas?

3. Method

3.1. Study design, Data collection:

A retrospective data collection was carried out between 2009 and 2021 in a single centre hospital.
All postnatal UTD recorded in the hospital software system (SAP) were retrospectively examined and the documentation illuminated with regard to the further development of CAKUT.
We checked all patient records for plausibility, duplicate coding, diagnostic pathway and clinical follow up. For each patient we recorded the patients characterica (see below)

We looked up whether these patients had already had any prenatal abnormalities during pregnancy. If known, we recorded when the pyelon dilatation first occurred (gestational week) and what extent was documented (AP Diameter in mm). This data was taken from the referral letters or the maternal medical history.
At the beginning of the study, the aim was to find out at which week of pregnancy these UTDs appeares, to what extent the AP Pyelondiameter and how the development proceeded during pregnancy.
Unfortunately, it quickly became clear that the retrospective data collection regarding the measurements of prenatal AP Diameter was very incomplete.
Therefore, the focus could not be placed on the prenatal development of a pyelon dilatation in relation to the later postnatal findings, we had to focus on the perinatal datas and detailed measurements of UTD (within the first 8 weeks of life).

Furthermore, the data for the perinatal time point (i.e. a few days after birth up to a maximum of 8 weeks of life) were selected. If ultrasound was performed during this period, then the extent of AP Pyelondiameter was documented. The ultrasound were all performed in our hospital, done by two different radiologists.

In the further follow-up, it was determined whether the patients had undergone surgery or not and what kind of surgical technique was used.

The further development with determination of the functional diagnostics or postoperative course were collected as data, but were only partially included to this analysis.
The long-term follow-up was important for the classification of the patients to certain categories according to the pathologies found. That`s why the entire patient file had to be studied for each patient.

The patients were assigned to the following categories:

- Transient UTD
- VUR
- Megaureter
- UPJO
- PUV

The following data were calculated: age at diagnosis, age until operation.

If the data were not known prenatal or perinatal, the patient was not included in the statistical analysis.

We assumed that relevant congenital pathologies seen prenatal at fetuses become clinically relevant within the first year of life. Therefore, only children were included in the evaluation who were diagnosed within the first year of life.

3.2. Criteria of inclusion/exclusion:

3.2.1. Inclusion criteria:

Patients who received codes of Hydronephrosis, PUV, UPJO, VUR, Megaureter, PUV, Duplex system, Dysplastic kidneys in SAP of our children hospital (single center) during periode of 2009- 2021. With the first patient contact, regardless of whether it is a prenatal consultation of the mother or a postnatal first consultation of the baby, the patient receives a code in the system.

3.2.2. Exclusion criteria:

- Children with syndromal conditions or perinatal complex conditions (such as perinatal asphyxia or renal pathologies arising in the context of multi-organ problems) which results in endstage renal disease.
- Acquired UTD (e.g. tumor, traumatic or iatrogenic) within the first year of life
- UTD in preterm infants below 36 SSW
- Neurogenic bladder (caudal regressions syndrome, MMC)
- If the children were older than 12 months when first diagnosed
- Patients with other renal structural pathologies like MCKD (multicystic dyplastic didneys) or Polcystic Kidney disease : ARPKD (autosomal rezessiv polycystic kidney disease)or ADPKD (autosomal dominant polycystic kidney disease)

3.3. Parameters collected and Patients Characteristica:

The following patientcharacteristics were analysed and included to this study:

- Sex: Male/female
- Age at Studytime
- Age at Operation
- Time to first Diagnosis (<12month)

AP Pyelondiameter prenatal known

- yes
- no or <4mm

AP Pyelondiameter postnatal (=perinatal, 0-8 weeks) known

- yes: AP Pyelondiameter 7-9mm
  AP Pyelondiameter >10mm
- no

Operation: yes or no

4. Statistics

The original data are taken from SAP Hospital Software.
For the analysis a Kaplan-meier curve was drawn up and the graphs created using Excel and SPSS.

5. Results

In the period of 12 years, we have treated 992 patients who had a single abnormality and received a UTD coding.

We have assumed that the time of diagnosis is relevant, i.e. if a child has an abnormal UTD above 12 months of age, an anatomical pathology such as UPJO, megaureter or PUV is unlikely. However, due to the time limitation of the examination data, there is certainly a high BIAS, especially in relation to the VUR. This is because VUR can also become conspicuous for the first time after 12 months of age.

This left a total of 416 patients who had received UTD coding within the first year of life.

5.1. Patients Characteristics

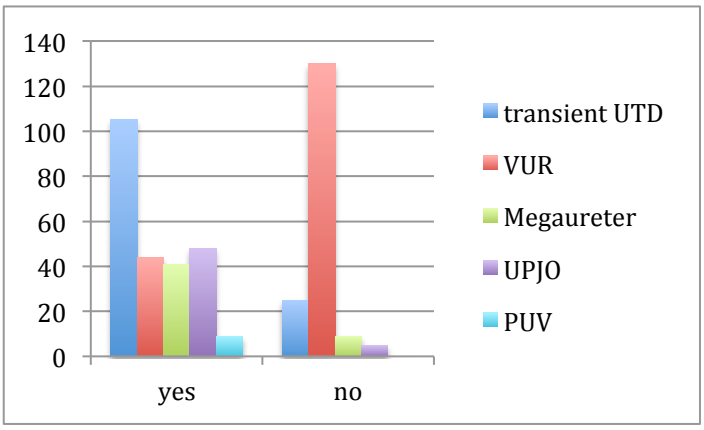
N*= 416	Number(%)
Male	278 (66)
Female	145 (34)
Age at Diagnosis (month)	4.8
Age at Operation (month)	11.8

5.2. Evaluation of AP diameter prenatal

Of these 416 patients, 247 (59%) were retrospectively known prenatal, 68% of whom received surgery during the follow-up.

N*= 416	Number	
Prenatal known		
• **Yes**	247	59%
• **no**	169	41%

Abb. 16 Prenatal known and different Pathologies



In contrast, 169 patients/fetuses (41%) were not known prenatal. However a certain misjudgement can be assumed here, as the prenatal documentation was partly inadequate (many unclear details in the retrospective data collection, details only known according to reports/documentation).
Prenatal ultrasound data are collected in the gynaecology department, stored on an internal system, these are not compatible with postnatal records in the children's hospital. Therefore, if the data were not correctly transferred to the report or were reproduced as a correct prenatal history, the parameters remain unknown.

In the following context we describe answers to our previously posed questions and hypothesis.

To refer the mentioned problems above we wanted to find out if our diagnostic pathway reflected the relevant patients who develop a CAKUT or defined pathology of UT.
We want to know if our datas are comparable to literature datas. → Yes our data are comparable to current data in the literature.

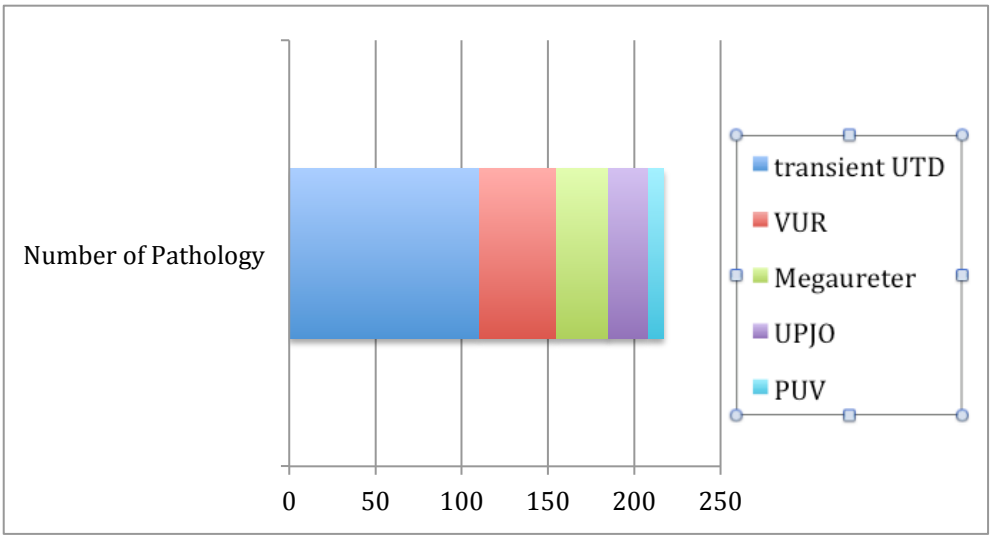


Abb 17 Number of Pathologies (in total)

** Pathologies found during 1-12 Month, all Patients.*

	Number of Patients identified with					
	transient UTD	VUR	Megaureter	UPJO	PUV	Unkown/ No
Number Pathologies*	116	45	36	41	9	135/34

5.3. Evaluation of the AP diameter at 3rd Trimenon

We wanted to evaluate if we decide with assumed AP Pyelondiameter prenatal >7mm as a valide cutt off in the 3rd trimenon? Due to the limited data available, it is not possible to make a statement about this aspect because we had a high number of unkown data of.

5.4. Evaluation of AP diameter at the date of birth/postnatal

How many children from a retrospectively collected database with postnatal diagnosed disease of UT were already known at birth? →Yes, we found that 152 (36%) of a UTD conspicuous at birth develop relevant pathology later in life

	Number of Patient identified with					
AP know postnatal (in total)	**transient UTD**	**VUR**	**Megaureter**	**UPJO**	**PUV**	total
7-9mm	35	4	8	4	3	54
>10mm* (*= 10-35mm)	37	21	22	36	5	121
unkown	12	103	9	11	0	135
0-6mm or not seen	46	46	11	2	1	106

We wanted to evaluate if the assumed UTD (urinary tract dilatation) with the cut off >7 is a valide parameter at birth.
How many of these patients with a dilatation 7-10mm develop later any pathological findings? → We detect 54 patients out of 416 (13%)

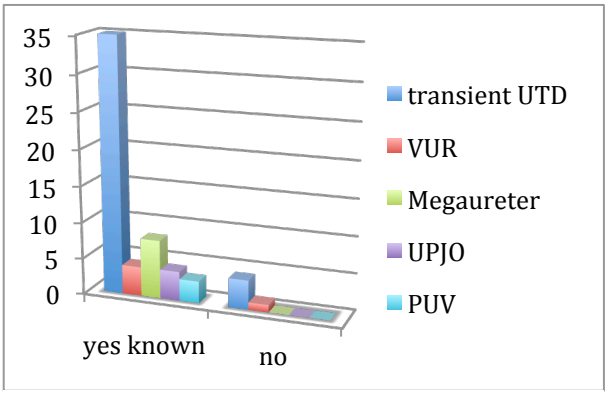


Abb. 18 Postnatal 7-9mm

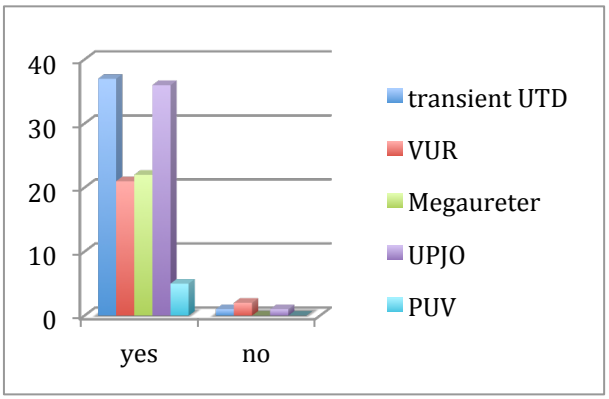


Abb. 19 Postnatal >10mm

	Number of Patients identified with					
AP know postnatal 7-9mm	**transient UTD**	**VUR**	**Megaureter**	**UPJO**	**PUV**	**total**
yes known	35	4	8	4	3	54
no	4	1	0	0	0	5

Do we find out with a cut off postnatal >10mm the same critical patients and how many of those develop pathological findings? → We would detect more pathologies in this group like 29% has shown any pathology (121/416)

Do we overdiagnose and alarm parents unnecessarily? → No it is important to look for the patients even with cut off 7mm. Of course the rate of transient UTD is higher in this group but we shouldn't miss 13% of the total quantity.

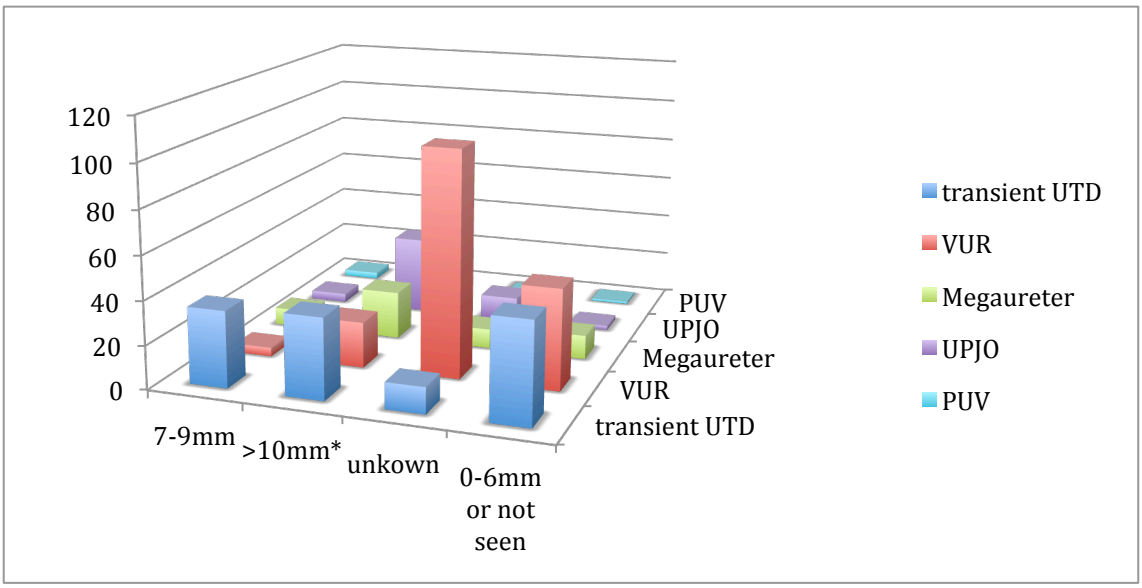


Abb. 20 Postnatal total Pathologies and AP Diameter ; * >10 (10-35mm)

Are there any other risk factors we can clearify with our datas? → Of the data collected, there are only a few valid data showing the prenatal development of pyelodilatation in pregnancy. Our impression is that an increase in UTD from the 2nd to the 3rd trimester of pregnancy seems to be relevant. Postnatal relevant pathological findings are often found in these fetuses, but the data set is to small to compare.

5.5. Development of pathologies over the time

We have seen that the children with PUV were almost 100% known prenatal (see limitations, Kap. 6.2.) or shortly after birth.

UTD transient also showed regressive findings in most cases within the first 4 months. The duplex systems took the most time to point of diagnosis.

Interestingly, Megaureter was diagnosed with about 4 months and UPJO was diagnosed after 6 months. This is probably related to the diagnostic work-up. In order to determine a relevant UPJO a functional diagnosis (MAG-3 Scintigraphy) must be made and this is usually done after 2-3 months of life. Of course in urgent cases, it can also be done after 6 weeks. In contrast, the diagnosis of a megaureter is made by ultrasound and exclusion of a VUR by VCUG.

VUR is diagnosed in a very variable time frame and there is certainly a high bias here (see limitation), since we only examined the children retrospectively up to the first year of life.

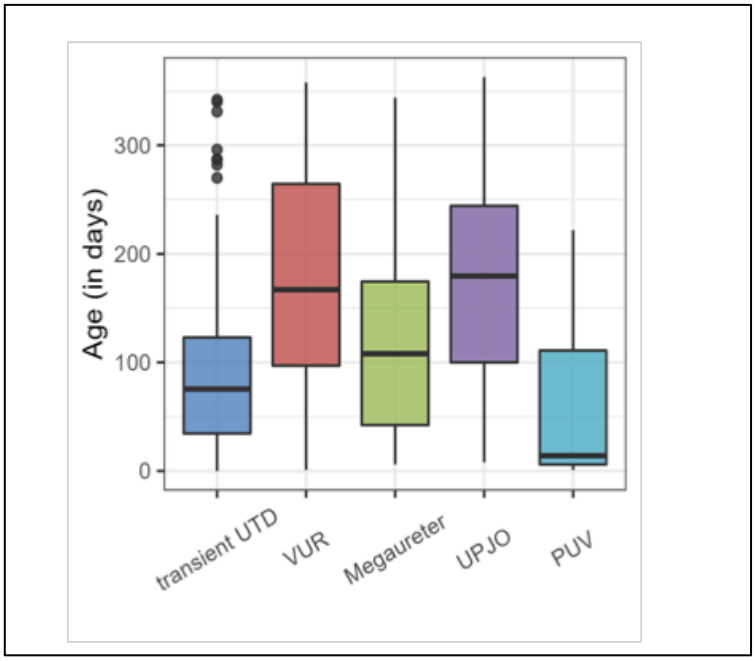


Abb. 21 Age at Diagnosis

Duplex System:
With regard to the duplex systems, it must be noted that these are usually noticeable if there is also another pathology such as distal ureteral obstruction, ureterocele, dysplasia of a pole system or ectopic ureteral position.
In the calculations, the duplex systems were seen separately, as there is usually a multiple pathology (e.g. duplex and distal ureteral obstruction).

Over the time you can see 75% of the Megaureter has been diagnosed 170d after birth. The diagnosis for UPJ was made only after 260d postnatally.

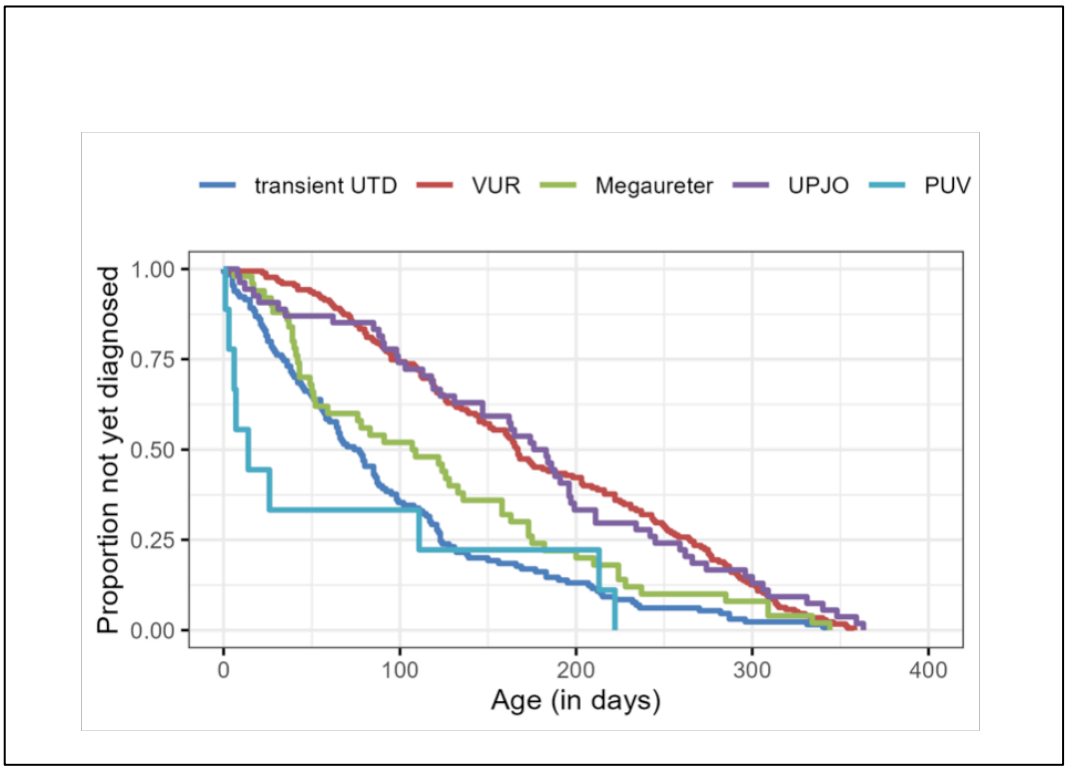


Abb.22 Diagnosis of Pathologies over the time (0-12 month)

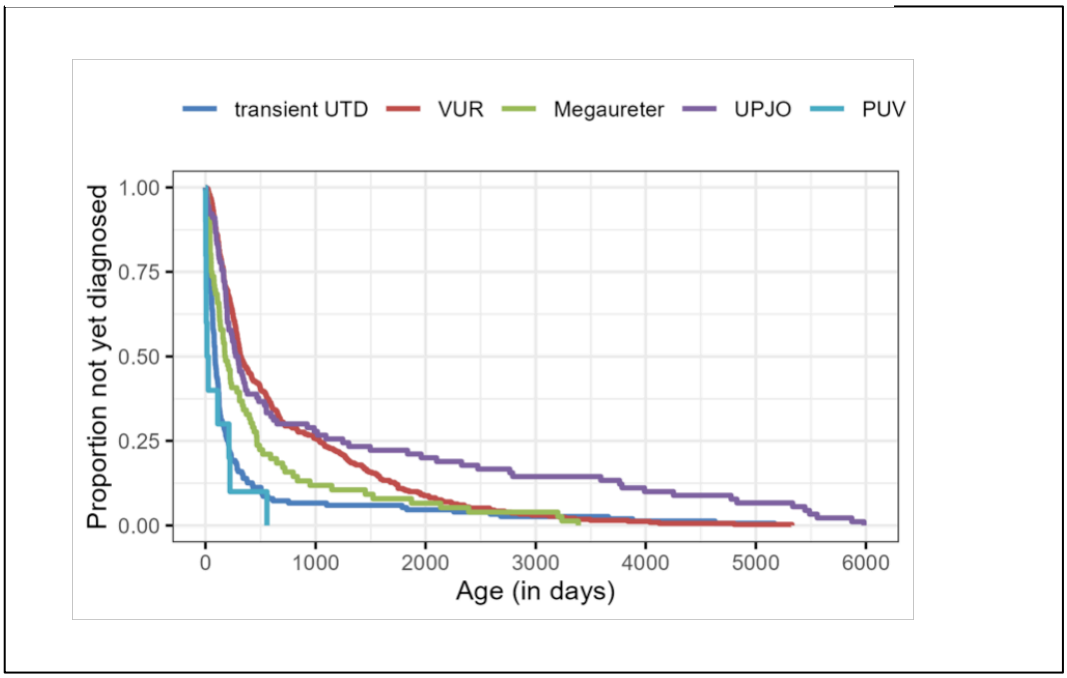


Abb. 23 Diagnosis of Pathologies over the time (0-18 years)

5.6. Pathologies and Surgery

Further on we wanted to know which patients have been treated conservatively and which patients received a surgery later in life.

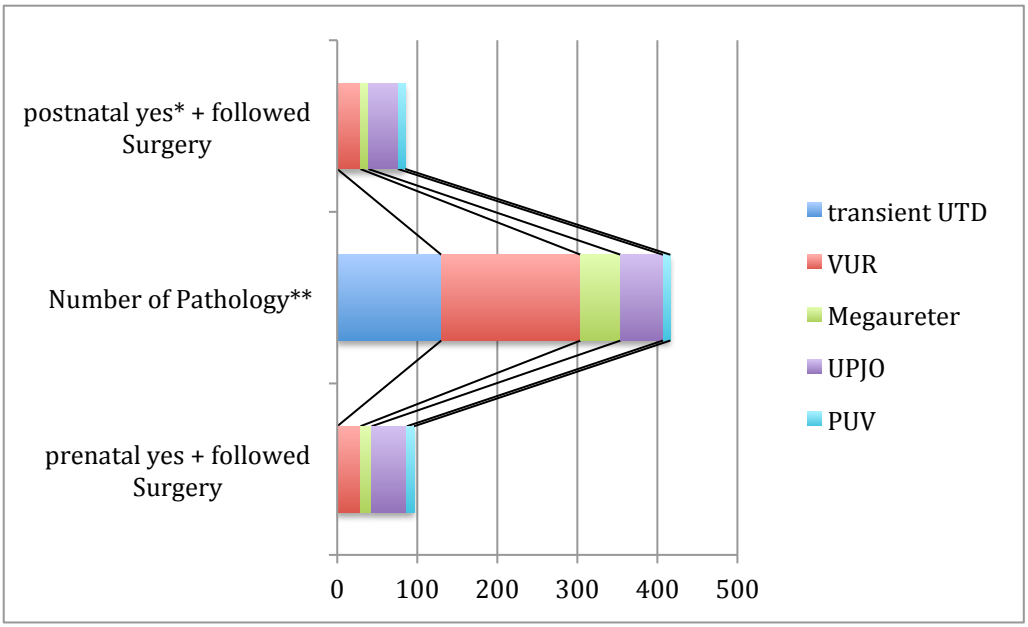


Abb 23. Pathologies and Surgery

According to our data set megaureter is treated conservatively in the majority of cases, regardless of whether it was known prenatal or not. Therefore, nothing can be said about the probable development of a megaureter that was already discovered prenatal.

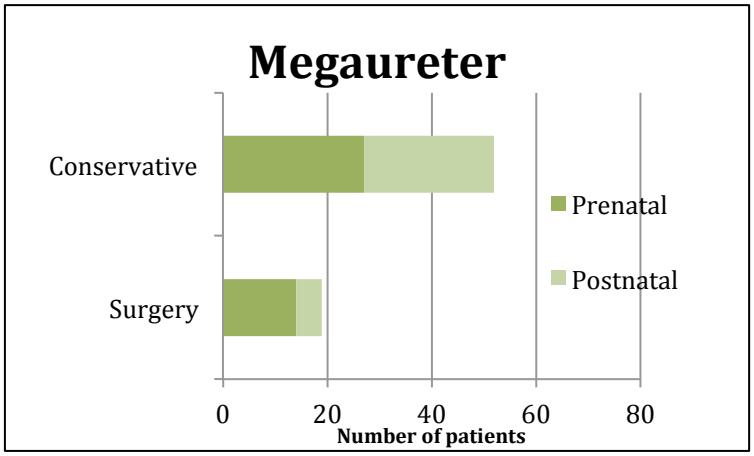


Abb 24. Megaureter and Surgery

If there is a prenatal suspicion that the pathology is due to UPJO the likelihood of surgery is very high.

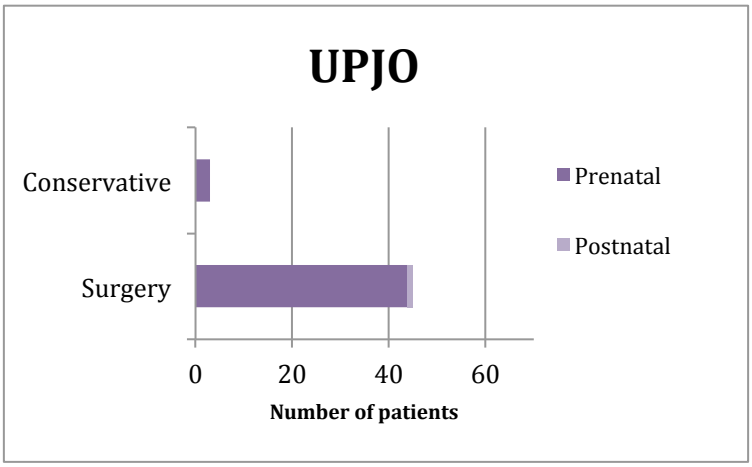


Abb. 25 UPJO and Surgery

VUR is most often detected in the unknown group at birth or prenatal. (see Abb. 20) This corresponds to the clinical experience and the literature.
In addition, we have to assume a misjudgement on regard to VUR, as we only included children in the study who were <12 months at the time of diagnosis. Since VUR often occurs later, it can be assumed that there is a pronounced BIAS.

6. Discussion:

6.1. Study data and review of the literature

The incidence of CAKUT is increasing for various reasons (see Annex, Incidence of CAKUT in European countries 1980-2017 (8).

Therefore the discussion about the postnatal management of prenatal UTD will be an ongoing discussion. (9)

Several studies has been performed to determine the best cutoff point of diameter of the renal pelvis leading to a pathology or even surgical procedure. Similar studies have been done in the direction on fetuses and infants.

Nguyen et al. (10) and Lee et al. (11) revealed that underlying etiologies of UTD included transient UTD (41% - 88%), UPJO (10% - 30%), Megaureter (5% - 10%) and VUR (10% - 20%). These ranges are comparable to our data in the study (Awith the exception of the VUR.

Nef et al. (12) showed that one third of the patients included in their study showed normalization of ultrasound findings, one third underwent surgery, and one third had persistent anomalies not requiring surgery . This underlines the generally good prognosis of most patients with suspicious kidney or urinary tract findings on fetal ultrasound examination

The development of AP Pyelondiameter at the end of the third trimester is probably similar to the values shortly after birth. Policiano et al. (13) showed concordance of intrauterine with postnatal diagnoses in 88.8% of cases . Thats why we focused on the ultrasound shortly after birth compare to the known data prenatal.

However even other studies attempting to define the normal range of measurements for the APD in pregnancy have found that the maximum dimension of the renal pelvis at any gestational age is <5 mm in 92.7% of fetuses and that it is reasonable to use an upper limit of 7 mm for the AP diameter in late pregnancy (14, 15, 16)

Many data has shown that a moderate PD of 7-10mm only 20-30% can be proven to have pathology during the course. With PD over 10mm, CAKUT is detected in the majority of 60-80%. (17) These data could also be confirmed in our study. With a postnatal measured AP 7-10mm we have detected in 35% and AP > 10mm in 69% of the cases CAKUT later in life. (Abb. 18 und 19)

Mallik et al. (18) has shown with a cut-off >10mm would reduce unnecessary consultations but 25% of those with UPJO hold-up and 50% with Megaureter and VUR would have been missed. But only 4/350 (1.4%) patients who has required an surgery of this group.

Abdulaziz et al. (19) reported that the best predictor for incurable UTD and the possibility of underlying pathology in postnatal AP Diameter equal to 5 mm had a sensitivity of 83%, equal to 7 mm had a sensitivity of 88% and 10 mm had a sensitivity of 94%.

Sharifian et al. (20)has shown that 23% patients of the prenatal recorded fetus needed surgery. In this study the best APD cutoff to predict surgery was 15 mm.

In our study we could underline that with a cut off >15mm perinatal, the UPJO is found in 96% and has needed surgery later in life. Further several studies has shown high sensitivity (73-100%) and specificity (82-86%) at a cut off > 15mm (21 Dias, 22 Coplen, 23 Kort).

This cut off is certainly out of the question and is described in the same way by many association and corresponds to the clinical experience.

There are several studies which have been identified certain parameters as indicators for the requirement of surgery. Arora et al has shown that APD and pre-operative DRF were the only independent predictors for requiring surgery, while cortical index and initial SFU grade of hydronephrosis were not predictiv (24).

The VUR is a pathology to be considered separately. We have included this pathology to this database for the sake of completeness. We know that VUR is the pathology with the worst concordance between prenatal diagnosis and postnatal outcome. This is known in the literature and is also confirmed in our study. (25) Furthermore, patients with intrauterine hydronephrosis and VUR seem to have a better resolution rate of VUR compared with patients first discovered to have VUR after a febrile urinary tract infection (11)

Duplex kidneys are another diagnosis often missed or misdiagnosed (26)
We can confirm this problem, Duplex systems are represented differently in all subgroups and are not very predictable. We had to examine them separately because they are often associated with multiple pathologies. Presumably this is the reason for a reduced prenatal detection rates for Duplex in the literature (27)

At the moment, the evaluation of a later occurrence of ESRD with known CAKUT in childhood is still pending in our study and subject of further studies. Calderon et al (28) found out that that the risk of ESRD among adolescents with a history of pyelonephritis was nearly four times as high as the risk among those with no history of childhood kidney disease

6.2. Limitations and Strength of the study

Limitations of the study is the retrospective character, we had no prospective study protocol.

In persistent UT dilatation with dynamic increase from the second to the third trimester, evidence of pathology appears to be more frequent.
It has shown for example that postnatal pathology (including VUR) was detected in only 12% of children with isolated second trimester UT dilation, but in 40% of those with dilation observed in both the second and third trimester (29)
In our data we could not prove this prenatal dynamic, we had to assumed a certain misjudgement, because the prenatal documentation was partly insufficient.
There are many unclear details in the retrospective data collection, accurate details are known only by according to reports/documentation, the orginal sonographic data was often no longer available or accessible. For example prenatal ultrasound data are collected in the gynaecology department, stored on an internal system, this ist not connected to the children's hospital, where postnatal records are stored. Therefore, if the data were not correctly transferred to the report or were reproduced as a correct prenatal history, the parameters remain unknown.
Thats the reason why we have in all categories an high number of unkown data.

The total number of cases of postnatal patients known with 7-9mm AP Diameter at birth is very small (n=54) and therefore only of questionable statistical significance.

Basically we have not changed our diagnostic pathway over the years to clarify transient UTD from pathological UTDs. In detail we initiated a VCUG less frequently in order to clarify the presence of a relevant VUR, so maybe the first diagnostic point of VUR is nowadays later in life than years before.
Only clarification process changed depending on the terminology, which is why we could only evaluate the extent of the AP Pyelondiameter and could not include the other risk factors (Abb. 5) classifications.

Recently we have changed the classification/ terminology to the UTD (P1-P3) classification and documentation included all parameters (Abb.5)
However, the coding (of hydronephrosis) has remained the same within the SAP and for the categorization this point should not have affected the dataset.

In our hospital the type of documentation changed from paper documentation to digital documentation and archiving of all data within the period under review.
In general, this made data collection easier, but it left a few data unclear that had been collected in other hospitals and had not been introduced into our new system. Thus, these data had to be declared as unknown.

The children with connatal PUV were almost 100% known prenatally. Interestingly, they were not always those with the greatest extent of AP Pyelondiameter or always

conspicuous prenatally. However, this also shows the variability of the diagnosis of PUV.
In addition, we have not taken into our data set the children with a late notice of urethral valve later in life. This is of course a considerable proportion of the total number of urethral valves diagnosed each year.

It would be interesting to determine from the data collected the percentage of patients with kidney function impairment due to congenital dysplasia or secondary dysplasia. We did not include other descriptive prenatal and postnatal risk factors (such as dilatation of the calices, parenchymal thickness or parenchymal appearance, ureteral dilatation or bladder abnormality) in our study.

The strength of our study is the continuous and close cooperation between the doctors caring for the prenatal and postnatal children and the data base over a long period of time. Over a long period, there were only a 2-4 doctors (radiologists, nephrologist, urologists) treating the patients with clear diagnostic pathway. Also the evaluation and discussion of prenatal ultrasound findings and maternal histories has taken place since a long time in weekly interdisciplinary meetings. Actually we are working on a fix framework of routine examinations pre- and postnatal (see Illustration)

6.3. Conclusion

Based on our data, we will continue to monitor patients with a perinatal AP Pyelondiameter of 7-10mm after birth in order not to miss the few cases that develop pathologies.

Future studies are important to consider the impact of prenatal counselling of an interdisciplinary team of Pediatric Urologist, Nephrologist, Neonatologists, Gynecologists and Radiologists.

We do need a simple classification system that correlates with clinical outcomes, the need for surgical intervention or renal function.
This classification system need to be implimented in all groups of medical professionals caring for parents of fetus and postnatal infant. They have to speak the same language.

The main issue will persist in future studies for prediction factors to clearify the outcome of an UTD and maybe restrict therefore further follow up diagnostics.

Perhaps we need to discuss what our goals are for postnatal outcome and management of antenatal UTD.
The individual pathologies are very inherent, the anatomy does not always correspond to our ideas and the temporal aspect plays a different role (e.g. in the case of a VUR compared to the case of a UPJO).
Perhaps we should differentiate the individual pathologies in order to inform parents, how high the risk for surgery is or can also be treated by conservative therapies or waiting.
We probably cannot get closer to the goal and look for different classifications, scores or grading systems that fulfill all these criteria at the same time.

7. Illustrations

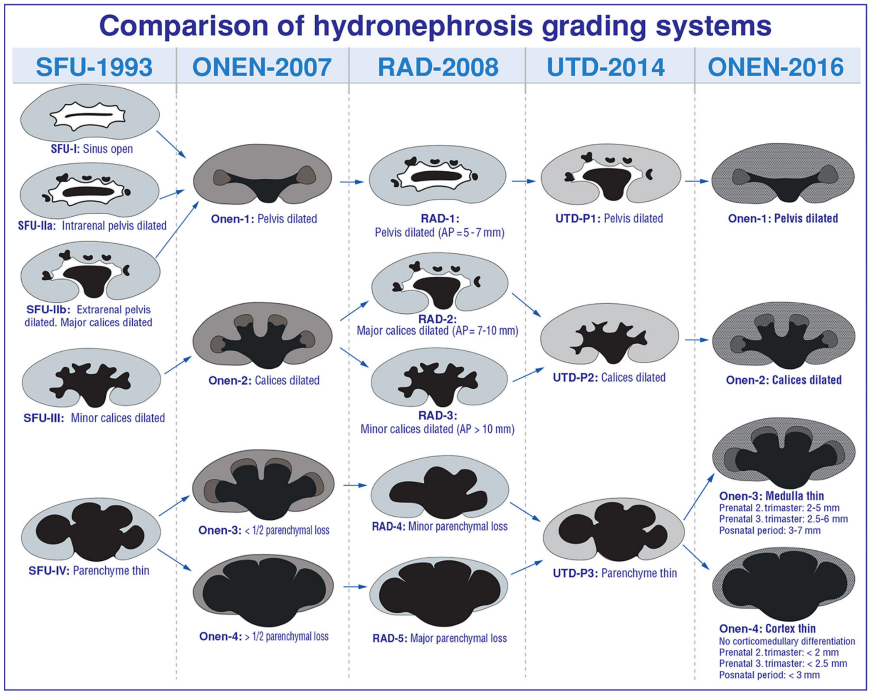
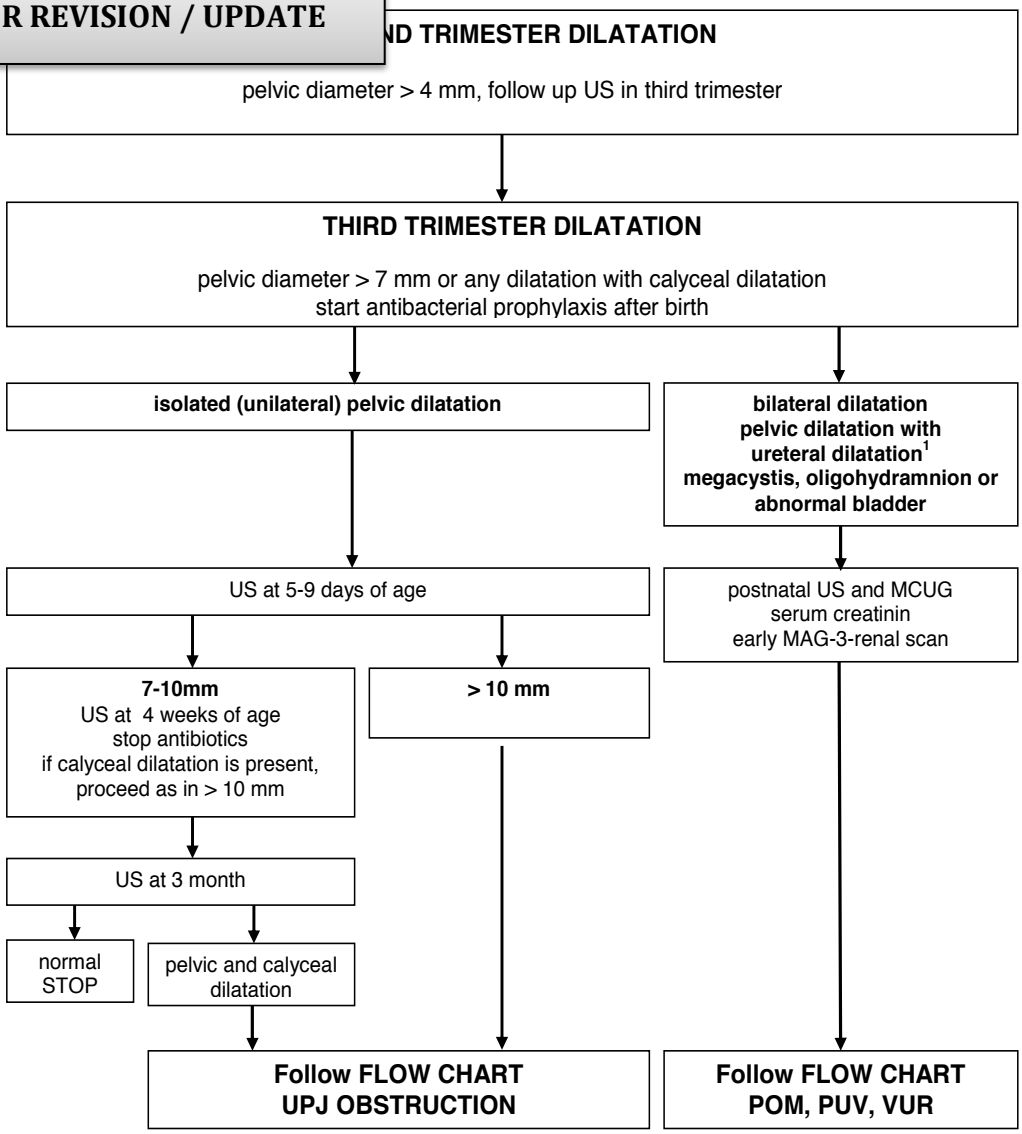


Abb. 26

A. Onen, Grading of Hydronephrosis: An Ongoing Challenge,Frontier of Pediatrics, 2020

Flow Chart: Prenatal Urinary Tract Dilatation / Prenatal Hydronephrosis

PLANNED FOR REVISION / UPDATE



[1] in girls with pelvic and unilateral ureteral dilatation the MCUG can be delayed till 4 weeks of age during which time prophylactic antibiotics are continued

Abbreviations

US ultrasonography
POM primary obstructive ureter
PUV posterior urethral valves
VUR vesicoureteral reflux
UPJ ureteropelvic junction

SwissPU January 2013

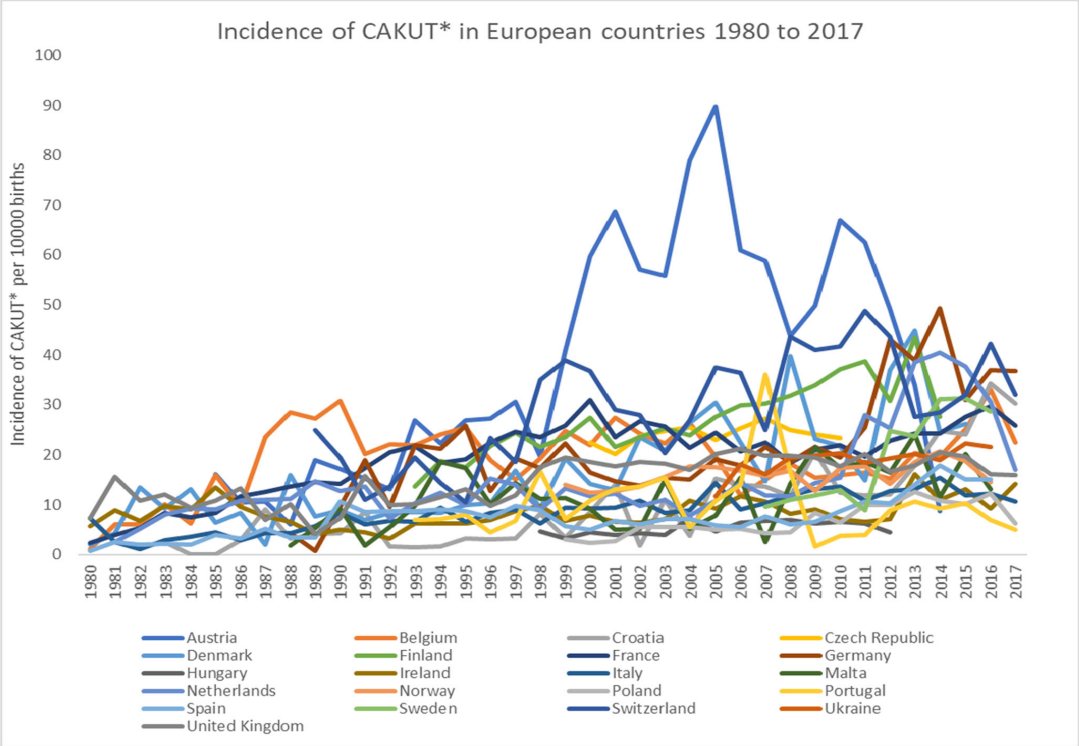
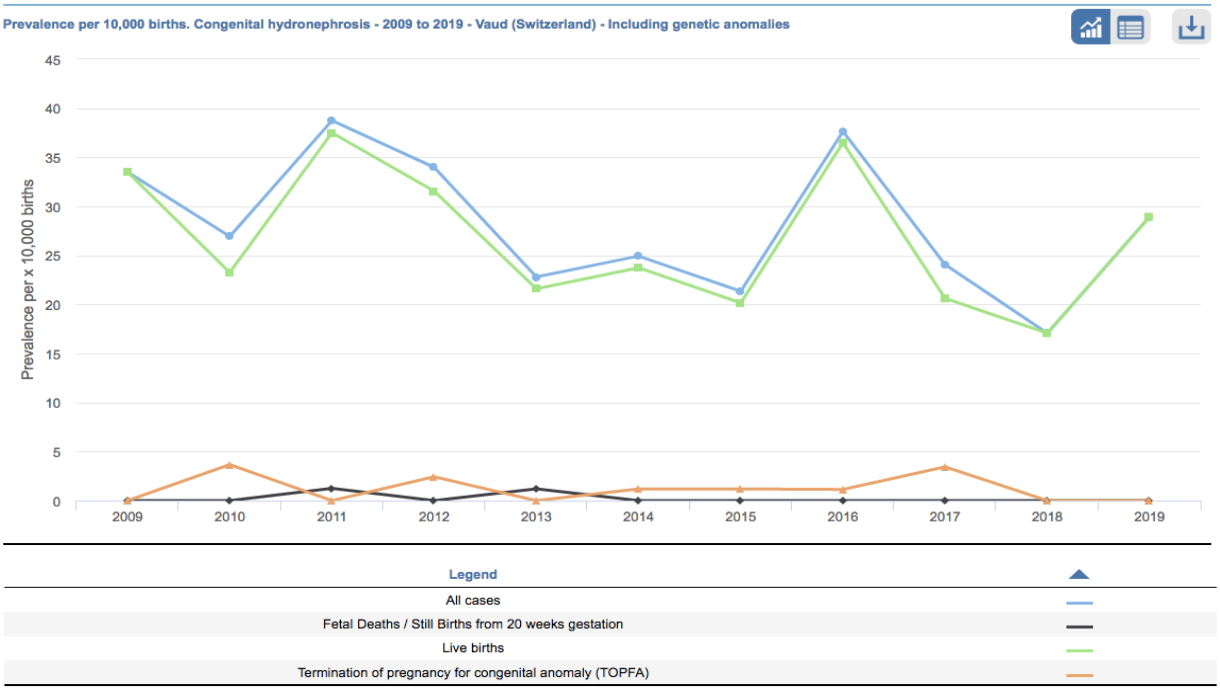


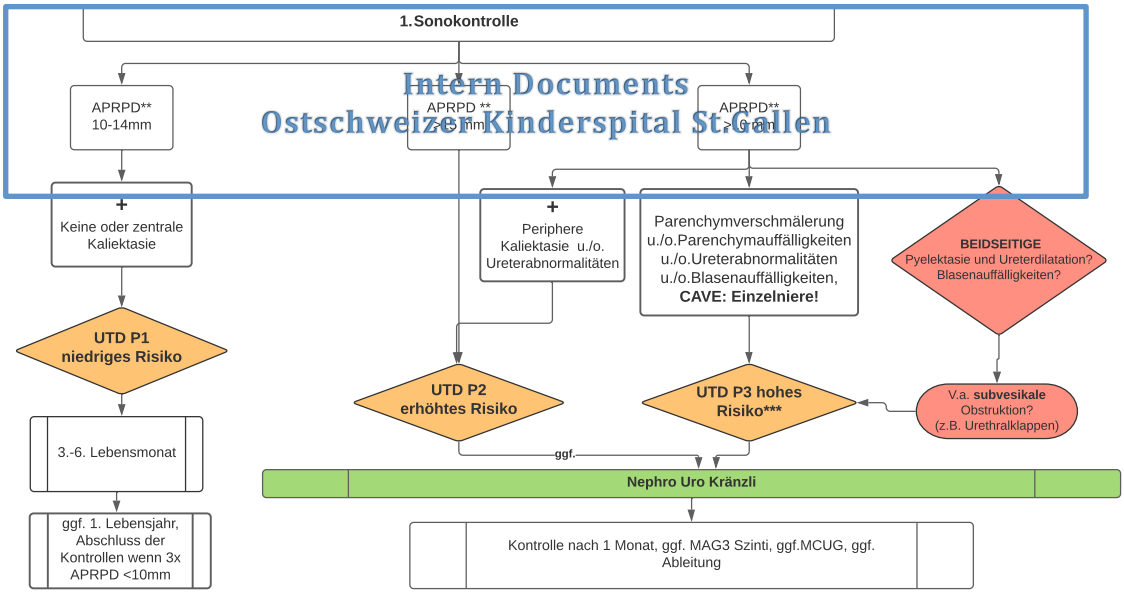
Fig. 4 Incidence of CAKUT* in European countries 1980 to 2017 (anomalies included in CAKUT: congenital hydronephrosis, posterior urethral valves, prune-belly syndrome, multicystic kidney dysplasia and bilateral kidney agenesis)

L. Jadresić , Pre-pregnancy obesity and risk of congenital abnormalities of the kidney and urinary tract (CAKUT)—systematic review, meta-analysis and ecological study, Pediatric Nephrology (2021) 36:119–132



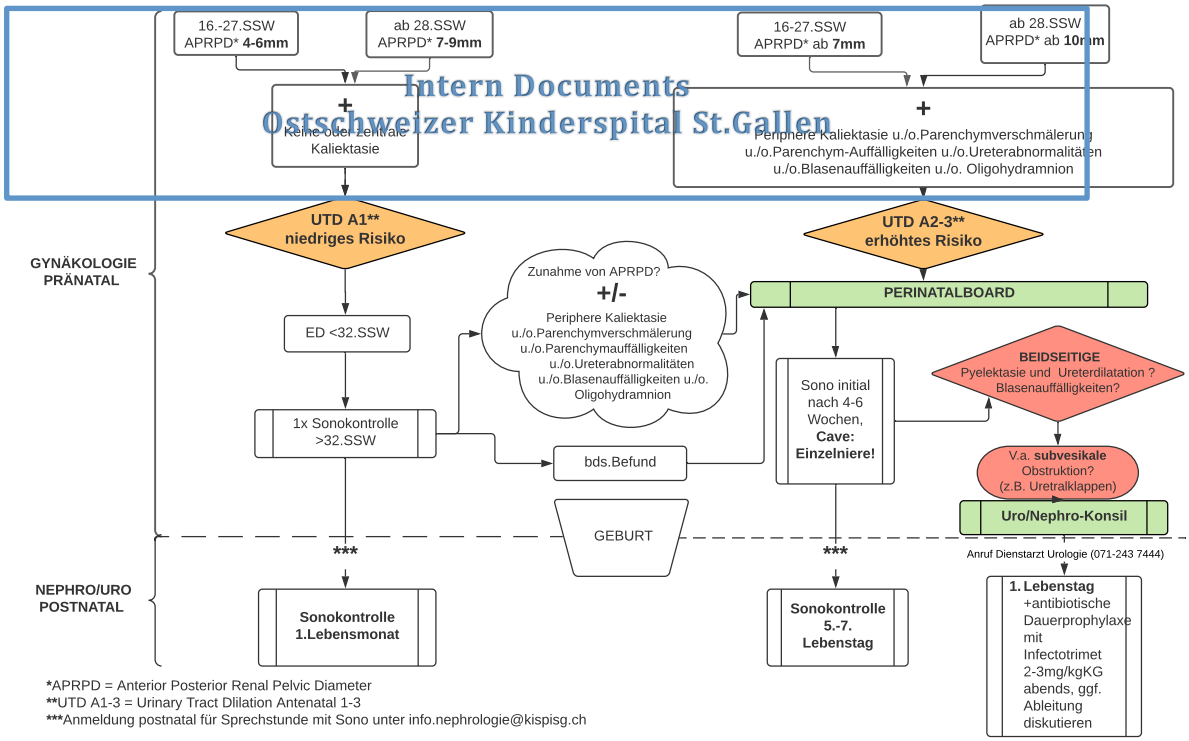
Incidence of congenital hydronephrosis 2009-2019 (Switzerland)
(*eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-data/prevalence_en*

DILATION DER HARNWEGE (UTD*)
POSTNATAL



*APRPD = Anterior Posterior Renal Pelvic Diameter
**UTD P1-3 = Urinary Tract Dilation Postnatal 1-3, falls neuer Befund: Email an info.nephrologie@kispisg.ch
***Beginn Antibiotikaprophylaxe mit Infectotrimet 2-3mg/kgKG in 1 ED abends bis zum Alter von 1 Monat, anschliessend TMP 2mg/kgKG in ED abends

DILATION DER HARNWEGE (UTD*)
PRÄNATAL



*APRPD = Anterior Posterior Renal Pelvic Diameter
**UTD A1-3 = Urinary Tract Dilation Antenatal 1-3
***Anmeldung postnatal für Sprechstunde mit Sono unter info.nephrologie@kispisg.ch

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9. Abbrevation

ADPKD	Autosomal dominant polycystic kidney disease
APD	Anterior Posterior Diameter
APRPD	Anterior Posterior Renal Pelvic Diameter
ARPKD	Autosomal recessive polycystic kidney disease
CAKUT	Congenital Anomalies of the Kidney and Urinary Tract
ESRD	End-stage renal disease
MAG-3	Diuretic 99mTc-mercaptoacetyltriglycine
MMC	Meningomyelocele
MRU	Magnetic Resonance Imaging
PUV	Posterior Urethral Valve
SFU	Society Fetal Urology
UPJO	Ureteropelvicjunctionobstruction
UTD	Urinary tract dilatation
VCUG	Voiding cystourethrogram
VUR	Vesicoureteral reflux

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