

Neonatal survival and kidney function after prenatal interventions for obstructive uropathies

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ABSTRACT

Objectives: Prenatal interventions in LUTO (lower urinary tract obstruction) usually are still question of a debate between gynaecologist and paediatric nephrologist. We aimed the study to assess the early survival rate and renal outcome in LUTO fetuses.

Material and methods: The study was a prospective data analysis of 39 fetuses from singleton pregnancies. All pregnant women with LUTO in the foetus were qualified for VAS based on a local practice. The mean time of first urine analysis ranged between 13–30 weeks of pregnancy. Primary end-point analysis included live birth, 28d-survival, pulmonary and renal function assessment in neonatal period.

Results: From initial number of 39, six patients miscarried before the procedure was performed. Overall, 33 VAS were performed at the mean 21 week of pregnancy (range 14–30 weeks). 25/39 fetuses survived until delivery. Three neonates died in first 3 days of life. In the first month 3 children required peritoneal dialysis, but at 28 day all children were dialysis-free. Overall survival rate at 28 day was 56%. Renal function preservation of the initial group (39) turned out to be low — 18% (7/39).

Conclusions: Our study showed average survival curves and complications. LUTO in the foetus had mostly unfavourable outcome in the neonatal period. The prenatal intervention did not increase it significantly and did not guarantee the preservation of normal kidney function.

Key words: obstructive uropathy; posterior urethral valves; vesico-amniotic shunting; kidney function; prenatal; neonate

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INTRODUCTION

Proper diagnosis and prenatal treatment of foetal lower urinary tract obstruction (LUTO) still constitutes a great challenge for obstetricians and neonatologists despite the significant progress in last 30 years [1, 2]. Clinically significant LUTO is detected in 1:10–20 000 pregnancies [3]. Male fetuses with posterior urethral valves (PUV) prevail, but

female fetuses may also develop LUTO due to urethral stenosis or atresia [3, 4].

According to the latest studies success rates measured by 2-y survival ranges from 21–72%, depending on the study intervention [5, 6]. It might be assumed that the long-term renal function depends mostly on the number of nephrons, dysplastic and cystic changes that had occurred before urine

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production start. This may be related to multiple genetic, epigenetic and environmental factors of early pregnancy, before any intervention is possible [7].

Prenatal interventions in LUTO usually comprise vesico-amniotic shunting (VAS) or laser valve ablation, which in selected cases are accompanied by amnioinfusions. These procedures may prevent pulmonary hypoplasia and progression of irreversible renal damage [3]. There was at least one attempt to prove the effectiveness of VAS in randomised controlled trial, but it did not show enough strength to draw firm conclusions [8]. However, some observational data and metaanalyses suggested that VAS may improve perinatal survival, but without significant influence of renal survival [9].

Because of the lack of randomised control trials and controversies about the interventions, there is still a place for observational trials in this field. Thus, the aim of our study was to assess the neonatal outcome in an unselected cohort of prenatally detected LUTO qualified for VAS.

MATERIAL AND METHODS

The study was a prospective observational trial (y.:2016–2018) led in the tertiary multidisciplinary reference centre on neonatal outcome in the cohort of fetuses diagnosed prenatally with LUTO and qualified for prenatal intervention. The study team comprised of 10 physicians (obstetricians, neonatologists, urologists and nephrologists), who were trained in the protocol.

The study was accepted by the Local Ethics Committee of Polish Mother's Memorial Hospital Research Institute (No:1/2016) and conducted according to the Declaration of Helsinki. All the pregnant women, and later parents and guardians of the neonates gave informed consents for participation in the study.

Inclusion criteria of the study were:

1. obstructive uropathy by ultrasound with megabladder detected in at least 2 separate examinations with or without hydronephrosis, with normal or reduced amniotic fluid volume

2. singleton pregnancy
 3. patient consent for prenatal intervention
- Fetuses with multiple genetic abnormalities and/or abnormal karyotype were excluded from further evaluation.

Study group characteristics

All the patients diagnosed with LUTO between January 2016 and December 2017 in whom the LUTO was detected by repeated ultrasound were offered a prenatal intervention of VAS and a prenatal and postnatal follow-up in the reference centre. The decision of prenatal intervention was based on clinical experience of an experienced obstetric team and the parents (local criteria for intervention: enlarged bladder, reduced amniotic fluid, hydronephrosis — uni or bilateral). The urinary analysis was done but did not constitute a contraindication for the intervention. Parenchymal kidney changes were noted but did not influence the qualification. Finally, 39 patients entered the study. Clinical characteristics of patients is presented in Table 1.

Preoperatively, a detailed ultrasound examination (Voluson E8, GE Healthcare) was carried out to confirm the diagnosis of obstructive uropathy and exclude any other major defects. Obstructive uropathy was diagnosed by the presence of enlarged bladder (megabladder) with or without "keyhole" sign. A diagnostic "keyhole" sign is seen in PUV, indicating continuity between distended bladder and the dilated posterior urethra proximal to the valves. Changes in renal parenchyma — increased echogenicity or structure and cyst formation were also described (Tab. 2). Oligohydramnios was defined by single deepest pocket of less than 2 cm.

Vesico-amniotic shunting procedure

Ultrasound scanning was used to obtain a transverse section of the enlarged bladder and define the appropriate site of entry on the maternal abdomen which was infiltrated with local anesthetic (10 mL of 1% lignocaine) down to the myometrium. Under continuous ultrasound guidance, the

Table 1. Prenatal characteristics of the study group. Continuous data presented as median value and min–max range)

	All fetuses N = 39	Survivors at 28d. n = 22	Non-Survivors n = 17	Statistical difference
Mother age [y]	29 (18–38)	29 (18–38)	29 (19–37)	> 0.05
Pregnancy	1.5 (1–5)	2 (1–5)	1.5 (1–3)	> 0.05
Week of diagnosis of LUTO	18 (12–30)	18 (13–30)	17 (12–21)	> 0.05
AFI [cm]	6 (0–21)	8 (0–21)	3 (0–21)	0.04
Week of intervention – shunting	21 (14–30)	22 (14–30)	20 (16–23)	0.06
Number of shunts/patient	1.5 (1–5)	2 (1–5)	1.5 (1–3)*	> 0.05
Need for amnioinfusions	18/39	12/22	6/17	NA

* only 11 were shunted; AFI — amniotic fluid index; LUTO — lower urinary tract obstruction

Table 2. Initial description of ultrasound images in the study group

Megabladder only	Megabladder and hydronephrosis	Only bilateral hydronephrosis	Renal parenchymal changes — echogenicity	Renal cysts present	Renal cysts or changes in echogenicity	Oligohydramnios
19/39 51%	14/39 36%	5/39 13%	22/39 56%	25/39 64%	29/39 74%	30/39 85%

Table 3. Biochemical predictive factors in the fetal urine analysis (median and min–max range)

	All subjects	Survivors at 28 d	Non-survivors	Statistical difference
sodium [mmol/L]	104 (50–146)	91 (50–146)	116 (50–127)	0.17
chloride [mmol/L]	84 (5–145)	80 (5–146)	95 (66–114)	0.17
B2–microglobuline	7.1 (0.4–24.7)	6.7 (0.4–17.0)	10.7 (2.2–24.7)	0.14
Osmolarity [mOsm/kg H ₂ O]	223 (96–289)	187 (96–289)	241 (164–264)	0.08

shunt (diameter 2 mm, length 12 cm; Rocket KCH Fetal Bladder Catheter, Washington, United Kingdom) was inserted.

In the foetal urine selected markers of prognosis were assessed: sodium (normal < 100 mmol/l), chloride (normal < 90 mmol/L), β 2microglobulin (SO-314.501 LIAISON beta 2- microglobulin; normal < 4.0 mg/L) concentration and urine osmolarity (normal < 200 mOsm/kg/H₂O). The values of these predictive indices in the study group are given in Table 3. They were analysed according to the criteria cited in the last review by Smith-Harrison [3]. Pregnancy duration and delivery procedures were analysed according to the outcome (demise, termination, still birth, live birth).

Neonatal assessment

After delivery the neonate was assessed with basic anthropometry and Apgar score. On the 4th day clinical and biochemical variables were analysed: survival renal function (eGFR and absolute creatinine [10]), albuminuria (albumin/creatinine ratio: ACR) and urine output, pulmonary function (ventilation dependency, clinical and radiological signs of pulmonary hypoplasia) and central nervous system (CNS) injury. Within first 28 days LUTO was confirmed/excluded by micturating cystogram/cystoscopy. Urologic interventions also were assessed. Clinical data were gathered with regard to the urine output, ventilation support and vasopressors need. Blood pressure was measured with oscillometric devices to exclude hypertension.

Urinary tract was assessed by a radiologist experienced in paediatric ultrasound. The Samsung RS80 device with convex/microconvex and linear probes were used.

Kidney injury was measured by serum creatinine (ELISA) compared with reference values of Rudd et al. [10] eGFR calculation was performed according to the Schwartz formula (with k value of 0.33 for neonates) and presence of albuminuria (albumin/creatinine ratio — ACR) [11]. Albumin excretion was compared to the data obtained in preterm

babies from the study of Gubhaju et al [12]. Children were tested for presence of acidosis. The study had 2 primary endpoints: survival and kidney injury symptoms at 28th day of life.

Statistical methods

Data analysis was performed using Statistica package version 12 (StatSoft Inc., USA) with medical add-in. All parameters were tested for normal distribution using Shapiro-Wilk W test and were presented as means with standard deviation. Comparisons of differences in characteristics between two groups (survivors and non-survivors) were performed using the Student's t-test and Mann-Whitney U test depending on the distribution of data. The differences between proportions were evaluated by chi-squared test.

The assessment of the validity of prenatal markers for 28-day survival was performed with discriminative analysis and a probabilistic predictive Naïve Bayes model. A Wilks lambda test was used to test for significant differences between the groups on the individual predictor variables. A significance level of $p < 0.05$ was considered significant. A receiver operating characteristic (ROC) curve with sensitivity and precision were applied to examine the correctness of the predictive model. The Kaplan-Meier estimator was used for estimation the survival function.

RESULTS

Amongst the study group all pregnant women accepted the prenatal intervention. However, six patients miscarried before the procedure was performed. Overall, 33 VAS were performed at the mean 21 week of pregnancy (range 14–30 weeks). No pregnancy lost was noted as a complication of prenatal interventions. In 6 cases there was a dislodgement/blockage of the shunt and procedure was repeated. Mean number of interventions was 1.5/foetus (range 1–5) — detailed data are presented in Figure 1. In 18 cases prior

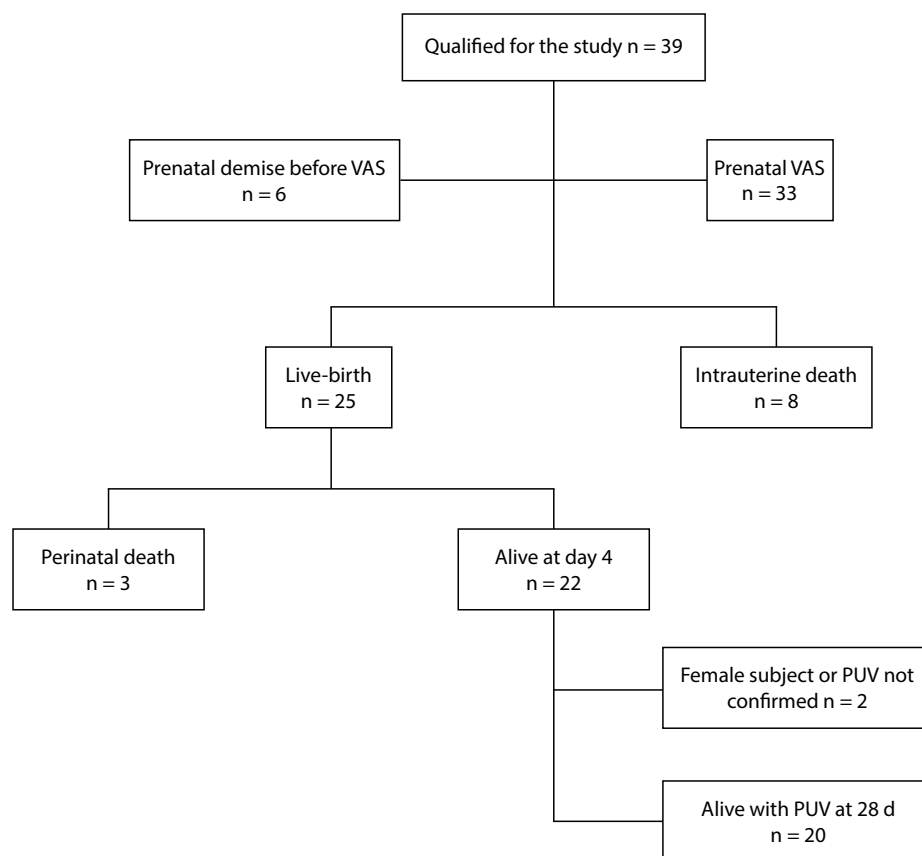


Figure 1. Outcome flowchart in the study group

to shunt insertion, amnioinfusion was performed due to technical difficulties (anhydramnios). Clinical characteristics of pregnancies are presented in Table 1.

20 patients were confirmed by postnatal evaluation to have PUV. In 10 fetuses diagnosis was confirmed by pathomorphology evaluation. There were also 1 urethral atresia (UA, in female) and in one no significant malformation of urinary tract was detected. There were 8 intrauterine deaths at mean age of 26 hbd (range 18–29). The deaths were noted with functioning shunts in a mean time of 3 weeks after shunting. 25 children were born at the mean age of 34 weeks (range 24–39 hbd) with mean Apgar score of 8 (range 1–10).

Anthropometrical, clinical and biochemical data of the live-born children with comparison of non-survivors and survivors at 28 day are presented in Table 4. We observed that those neonates who died after birth had lower birth age, body mass, head circumference and Apgar score.

Radiological and clinical investigations confirmed LUTO in 24/25 newborns (PUV-23, UA-1). 6 children had urinary tract diversions in neonatal period and 16 cystoscopy with electroresection of the PUV within 28 days. No patient had hypertension. 21/25 required intensive care with cardiac support with vasoactive amines and ventilation support (for the mean 2.4 days — range 1–20). Mean ICU stay was

36 days (1–150 d.). Radiological features of lung hypoplasia were detected in 6/25 neonates. We noted 3 deaths within first 3 days of life because of cardio-pulmonary insufficiency with lung hypoplasia. At 4th day 18/22 required mechanical ventilation but at 28th day all children were free of mechanical support. In 2/22 clinical features of pulmonary hypoplasia were present at this time. No child amongst those who survived required oxygen supplementation at the end of neonatal period.

Renal function was compromised in 13/22 of subjects who survived with mean eGFR on 4th day of 16.2 (4–47) mL/min/1.73 sqm. Serum creatinine was elevated also in 13/22 when compared to the reference from 7th day published by Rudd. [10]. 12 out of 22 neonates had significant acidosis and 11/22 proteinuria (mean: 102; r: 25–339 mg/dL). ACR was significantly elevated in 86% of cases (Tab. 4).

Three out of 25 (12%) children were treated with peritoneal dialysis at 4th day (for 3 to 19 days) – and all survived, while no one required it at the 28th day because of renal function improvement.

Overall survival rate at 28th day was 56% among whole LUTO group of patients. In PUV patients it was lower 20/37 — 54%, but in those who underwent VAS — 20/30 — 66%.

Table 4. Clinical and biochemical characteristics of neonates from the study group (median and min–max range)

	All subjects	Survivors at 28d	Non-survivors (demise/ stillbirth/death)	Statistical difference
OU confirmed	38/39	21/22	10/17*	NA
Gender (M:F)	38/1	21/1	17/0	NA
Birth age [weeks]	33 (24–39)	35 (29–39)	30 (24–32)	0.001
Apgar score at 5 min.	8 (1–10)	9 (4–10)	6 (1–6)	0.001
Weight [g]	2.4 (0.5–4.4)	2.6 (1.5–4.4)	1.8 (0.5–1.9)	0.005
Length [cm]	47 (28–57)	49 (41–57)	41 (28–42)	0.002
Head circumference	31 (15–38)	32 (27–38)	30 (15–32)	0.002
Ventilation support after birth [%]	21/25	18/22	3/3	NA
Oxygen dependency at birth [%]	24/25	21/22	3/3	NA
Pulmonary hypoplasia at 28 d [%]	NA	2/22	NA	NA
ACR at 4 d [mg/mg]	NA	7.7 ** (2.6–30)	NA	NA
Serum creatinine at 4d [mg/dL]	NA	1.7 (0.5–1.74)	NA	NA
eGFR at 4 d. [mL/min/1.73 BSA]	NA	10 (4–37)	NA	NA
ACR at 28 d [mg/mg]	NA	4.7*** (0.05–13.5)	NA	NA
Serum creatinine at 28d [mg/dL]	NA	0.95 (0.25–4.7)	NA	NA
eGFR at 28d. [mL/min/1.73 BSA]	NA	20.6 (5–79)	NA	NA
Urine output [mL/kg/h] at 4 d	NA	3.4 (1.0–7.5)	NA	NA
Dialysis need [%]	3/25	3/22	0/3	NA
Dialysis length [d]	3–19	NA	NA	NA
ICU stay [d]	NA	19 (1–150)	NA	NA
Acidosis at 28day	NA	9/22	NA	NA
HCO ₃ [mmol/l]	NA	10 (17–25)	NA	NA

* — only 10 were analysed by pathomorphology; ** — maximum excretion for preterm 0.21 mg/mg (22 mg/mmol) by Gubhaju et al. [12]; *** — maximum excretion for preterm 0.11 mg/mg (15 mg/mmol) Gubhaju et al. [12]; eGFR — estimated glomerular filtration rate; NA — not applicable; OU — obstructive uropathy

Kidney injury markers were also tested at the end of neonatal period. 12/22 (54%) neonates had impaired eGFR (13/33 elevated creatinine) with eGFR of 24 (range 5–19) mL/min/1.73 m²BSA, 18 (82%) had increased albumin excretion (mean 5.4 range 0.05–13.5 mg/mg). When the combined renal survival (free of any injury) of the initial group (39) was analysed, it turned out to be significantly low — 18% (7/39). When only who survived neonatal period were qualified the percentage rose to 32% (7/22).

When we compared the data of foetuses (children) who survived with the other only several significant differences were detected. Normal foetal urine osmolarity was detected in 10/22 foetuses who survived and in only 1/17 who did not ($p = 0.03$). We also found that in the former group AFI was higher (8 vs. 4, $p = 0.04$). Borderline significance was achieved with the age of the first VAS (21 vs. 19 hbd, $p = 0.056$).

We aimed at determining any prenatal marker of 28-day survival in the study group. Clinical markers of the pregnancy and VAS intervention, sodium, chloride, β_2 -microglobulin urine concentration, urine osmolarity, amniotic fluid index,

presence of dysplastic changes in renal parenchyma were initially included. Using common statistical tests and discriminant analysis, we only found that the survival rate was higher in those who were shunted. To validate the discriminative quality of shunting for prediction of survival we used a probabilistic predictive Naïve Bayes model. The assessed sensitivity the model was of 0.718 and precision of 0.812 with a low value of AUC equalled 0.528. The combination AFI, shunting and normal urine osmolarity assessed at the moment of diagnosis were characterised similarly: sensitivity of 0.744, precision of 0.743 with AUC 0.850. No other single predictor or combination of predictors were recorded as prognostic.

In the Kaplan Meyer analysis at 28th day we observed that foetuses with at least 2 (out of 3 standard) abnormalities in the urine analysis differed with regard to outcome (Fig. 2).

DISCUSSION

We aimed our study to assess short-term outcome in LUTO. The patients remained under care of the same team

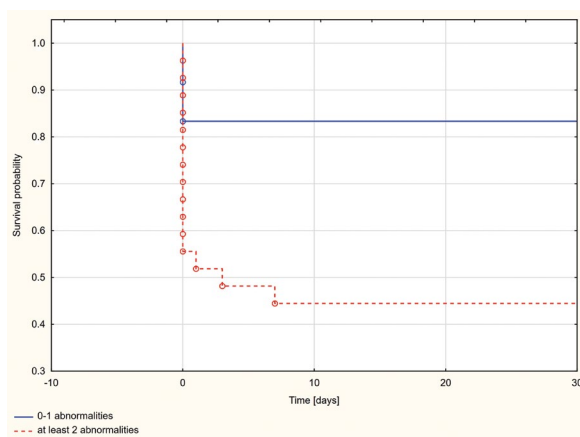


Figure 2. Kaplan-Meier survival curves for all subjects and adjusted to the presence of negative prognostic factors in fetal urine analysis

until the end of pregnancy and at least up to 28th day after delivery.

Prenatal diagnosis was confirmed in 87.6% cases. We found that overall survival rate in LUTO qualified for shunting at 28d was 56%, however when only shunted foetuses were included it rose to 66%. When the renal function preservation was analysed, we showed that significant number of children had compromised eGFR at 4th day from delivery with need for temporary dialysis in 3/22. Proteinuria in this group of patients was also a frequent marker of kidney injury. Only 18% of initially qualified subject survived until neonatal period with no kidney injury (eGFR decrease or significant proteinuria). VAS preserved renal function in 7/22 children who survived (32%). The overall 28d survival rate was similar to those reported in other single and multicentre trials.

The analysis conducted by Morris et al. done on basis of PLUTO randomised controlled trial and prospective observational cohort study reported 28 day survival rate as 50% and 40% respectively [6]. What was surprising, this survival rate was significantly lower than in the conservatively managed patients. Survival to 28 days after delivery was higher in the conservative-management group, at 69% (24/35), compared to 40% (4/10) in the VAS group ($p = 0.02$). Compared to the conservative-management group of the trial, a higher proportion of women in this registry opting for conservative management had a normal amniotic fluid volume at diagnosis ($p = 0.05$) and a diagnosis of LUTO ≥ 24 weeks' gestation ($p = 0.003$). On multivariable logistic regression analysis, these variables showed a significant association with perinatal survival ($p < 0.001$) [6].

Ruano group assessed the 2-y outcome after foetal intervention in 50 patients with LUTO. They found PUV in 31 (62%) foetuses, urethral atresia (UA) in 14 (28%) foetuses, and urethral stenosis (US) in 5 (10%) foetuses. There were no survivors in the UA group. Eleven (22.9%) infants died during

the neonatal period because of prematurity, lung hypoplasia or renal failure [13]. Short term survival rate in all abnormalities was 36% (18/50) which is comparable to our data.

Ethun et al. [14] analysed outcome of 14 patients after prenatal intervention of LUTO and showed similar results to our observation with regard to success and complications. Jeong et al. [15] showed among the 32 foetuses examined that: 5 died because of termination of pregnancy, and 2 died in utero. Three neonatal deaths occurred, resulting in an overall perinatal survival rate of 68.8% (22 of 32). Fontanella et al. [16] analysed the data of foetuses at high-risk of isolated LUTO and managed conservatively. The survival rate was 42% and was similar to our observation. Martinez et al. performed 20 fetal PUV ablations at the median gestational age of 18.1 weeks (range 15.0–25.6). Overall, there were 9 (45%) terminations of pregnancy and 11 women (55%) delivered a liveborn baby at a mean gestational age of 37.3 (29.1–40.2) weeks. No infants who survived developed pulmonary hypoplasia and all were alive at 15–110 months [17]. Johnson et al. [18] in the cohort study on LUTO in USA reported even higher percentage of perinatal survival (97%), but surprisingly dialysis was required in 32% of patients.

Ruano et al. analysed retrospectively a cohort of 111 foetuses with LUTO. They showed that the probability of survival was significantly higher with foetal cystoscopy and VAS when compared to no intervention [adjusted relative risk (ARR) 1.86 (95% CI, 1.01–3.42; $p = 0.048$) and ARR, 1.73 (95% CI, 1.01–3.08; $p = 0.04$) respectively]. Unfortunately, there was no statistically significant chance for maintaining normal kidney function in short and long-term observation. However, when they analysed only PUV patients, the situation turned out to be more optimistic. Foetal cystoscopy was effective in improving both the 6-month survival rate and renal function [ARR 4.10 (95% CI, 1.75–9.62; $p < 0.01$)] and 2.66 [(95% CI, 1.25–5.70; $p = 0.01$) respectively] while VAS was associated only with an improvement in the 6-month survival rate [ARR 3.76 (95% CI, 1.42–9.97; $p < 0.01$)] with no effect on renal function (ARR 1.03 [95% CI, 0.49–2.17, $p = 0.93$]) [5].

We found that shunting with VAS was successful in prevention of renal injury in the neonatal period only in 18% of patients from the initially qualified group. From those who survived 32% were free of any injury. In the study of Martinez et al. [17] on 20 PUV ablations, 8 (40% of all foetuses, 72.7% of newborns) had normal renal function and 3 (27.3%) had CKD awaiting renal transplantation. They assessed the kidney injury by eGFR decrease with no data on proteinuria. Similarly, Ruano et al. [13] reported that among the infants with PUV 17/30 (56.7%) survived and 13/17 (76.5%) had normal renal function at 1 year of life; 15/28 (53.6%) survived and 11/15 (73.3%) had normal renal function at 2 years.

Our study showed that classical prognostic factors did not differ between the survivors and non survivors group.

Only a combination of predictors (shunting, urine osmolarity and AFI) showed little value in this prediction. In the Kaplan-Meier curve analysis fetuses with at least 2 increased classical biochemical parameters (osmolarity, sodium and chloride concentration) had lower survival rate. These results are concordant with other studies, where only combined prenatal factors were potentially qualified as significant in multivariate analysis [5, 14, 18, 19].

We are aware of the weaknesses of the study. The number of patients included was relatively small, but that was a single centre analysis. Only multicentre studies presented significantly higher number of patients. Furthermore, there was no comparator (conservative treatment) arm in the study group, nor the randomisation was possible. However, this weakness may turn into some strength. Because of specific treatment policy of the centre and profile of the country our cohort was complete and all of the pregnant women with LUTO diagnosis referred in second trimester were proposed an intervention with no option of termination of pregnancy based on patient decision. The number of patients at the first sight would look low, but when it is compared to single arms of PLUTO studies and other papers it could be qualified as one of the largest prospective cohort of VAS ever published [6]. One can postulate that the location of neonatal and urology-nephrology centre in once place increases the value of observation and quality of data. The data gathered in the neonatal period concerning comorbidities and development should enrich the value of observation. The broad range of VAS intervention (up to 30 week) also decreases the precision and value of observation but similar approach was also presented by other authors.

CONCLUSIONS

Our study led to clinically important conclusions that pregnancies with LUTO fulfilling criteria for prenatal interventions had significant percentage of unfavourable outcome. The full prevention of the kidney injury in live-born subject was difficult to achieve. However, the need of early neonatal dialysis was relatively low.

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Conflict of Interests

The authors declare that they have no conflict of interests.

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