MAR Pediatrics **(2024)** *5:8*

Research Article

Contrast Enhanced Voiding Urosonography versus Conventional Voiding Cystourethrography

Dr. Vishal Chandrashekhar Ghattargi[*1] , Dr. Saroj Rathod[2], Dr. Pradnya Bendre[3]

1. M.B.B.S; M.S General Surgery, M.Ch Pediatric Surgery, Fellowship Pediatric Urology.

2. M.B.B.S; DNB Radiology; DMRD

3. M.B.B.S; M.S General Surgery, M.Ch. Pediatric Surgery; DNB Pediatric Surgery; MBA hospital administration; PGDMLS.

*__Correspondence to:__ Dr. Vishal Chandrashekhar Ghattargi, Department of Pediatric Surgery

Bai Jerbai Wadia Hospital for Children, Parel, Mumbai.

Received: 29 Nov 2024

Published: 20 Dec 2024

Abstract

Aim: To assess the efficacy and feasibility of ultrasound guided voiding cystourethrography as a standard investigating procedure for diagnosis of VUR in day-to- day practice.

Material and Methods: This is a single centre cross sectional study of all the newly diagnosed and managed cases of vesicoureteric reflux under the age of 5 years by Department of Paediatric Urology in Bai Jerbai Wadia Hospital for Children, Mumbai. The demographic details, clinical presentation, investigations and results were tabulated, collated and analysed.

Results: 39 refluxing units were studied in 30 diagnosed cases of VUR (M-19, F-11). Besides those detected antenatally (13), patients presented with recurrent UTI's (08), dribbling micturition (05) and bowel bladder dysfunction (04). Anomalies associated with reflux were PUV (12) and Neurogenic bladder (02). Contrast enhanced voiding urosonography is not only efficient and feasible but also safe in evaluation of VUR compared to the current gold standard technique.

Conclusion: Contrast-enhanced voiding urosonography using intravesical ultrasound contrast agent is a valid alternative diagnostic modality for detecting vesicoureteric reflux, based on its radiation-free, highly efficacious, reliable, and safe characteristics.

Introduction

Urinary tract infection (UTI) is a common emerging paediatric condition. It has a multifactorial etiology, with multiple host factors implicated in its pathogenesis. Vesicoureteric reflux (VUR) is known to be one of the most important associations of paediatric UTI. Vesicoureteric reflux is the retrograde flow of urine from the bladder into the renal collecting system. It provides a pathway for ascent of bacteria and along with infection results in renal scarring. The incidence of VUR in children with UTI is nearly 30% to 40% (1). Intrarenal reflux can lead to renal scarring, and repeated episodes of UTI can lead to deterioration of renal function, renal failure, and even hypertension.

Currently, various modalities are available for reflux diagnosis like voiding cystourethrography (VCUG), radionuclide cystography (RNC) and voiding urosonography (VUS). Voiding cystourethrography and radionuclide cystography are the traditional diagnostic procedures used for this purpose. Voiding cystourethrography is a universally accepted modality for the diagnosis of VUR. However, it does involve catheterization and exposure to radiation thus making it an invasive and unpleasant investigation. Ultrasound is an alternative imaging modality for the pediatric population. It does not involve ionizing radiation and is well tolerated by the young. Ultrasound guided procedure is carried out using US in combination with intravesical administration of US contrast agent (UCA). This prevents the patient from exposure to ionizing radiations, which is not the case in RNC and VCUG.

The first attempts at the implementation of US for the diagnosis of VUR began in the mid-1970s. A comprehensive account of the evolution of this undertaking over the subsequent two decades has been presented by Darge (2). Different methods were utilized for the diagnosis of the pathology. The indirect methods for reflux diagnosis were based on US of the urinary tract, without administration of any kind of substance into the bladder.

These included depicting various changes of the urinary tract seen on ultrasound as a result of VUR like detecting newly appearing or an increase in existing ureteral or pelvicalyceal dilatation during voiding and assessing ureteric jet changes with duplex and colour Doppler US. On the other hand, direct means used to diagnose VUR required instilling different substances intravesically. The most commonly administered fluid was physiological saline solution. Changes like ballooning of the renal pelvis during the filling of the bladder was considered as the criterion for diagnosis of VUR (3). Other techniques like application of air bubbles, by shaking the normal saline before administration or adding carbon dioxide, were also tried. Ultrasound studies were also carried out, in which the empty bladder was solely filled with air. In addition to low diagnostic accuracy, all the above methods had major procedural drawbacks making them impractical for widespread integration into routine imaging.

The intravesical use of a UCA consisting of sonicated albumin (Albunex; Molecular Biosystems, San Diego, Calif.) for VUS in a child was first reported in 1994(4). Another UCA used in the past was Echovist (Schering, Berlin, Germany), which is composed of galactose with incorporated microbubbles (5). It’s very short imaging window of approximately 5 min, however, prevented its routine application. The breakthrough in US diagnosis of VUR in children came about the mid-1990s with the availability of UCAs containing stabilized microbubbles. Levovist (Levograf, Schering Spain, Madrid, Spain; SHU-508-A, Schering, Berlin, Germany) was the first such UCA to become available for clinical use in Europe. This opened the door for rapid development of VUS and its introduction as part of the routine diagnostic imaging option of VUR. A number of different names and acronyms have been put forward to denote US examination for the diagnosis of VUR using intravesical UCAs. These include simply "sonography/ultrasound" (6-8), "reflux sonography"(9), "cystography"(10-12), "cystosonography"(13-17), "cystourethrosonography"(18) and "urosonography"(19-25).

Ultrasound-based reflux imaging has been investigated in Europe for over more than 20 years (26). It is now called 'contrast-enhanced voiding urosonography' (ceVUS), previously known as reflux sonography, echocystography, cystosonography, and echo- enhanced cystography (9,11,15). The ceVUS is technically analogous to conventional MCU, in that an ultrasound contrast agent is administered intravesically via the urinary catheter, followed by continuous, alternate examination of the kidneys, urinary bladder, and retrovesical region during filling and voiding phases, as well as the urethra via transperineal or interscrotal approach during voiding phase.

The diagnosis of vesicoureteric reflux is determined by the presence of moving echogenic (bright) microbubbles from ultrasound contrast in the upper urinary tract. Its five-tier grading system by Darge and Troeger (27) is similar to the international reflux system, based on the presence of reflux and dilatation of the collecting system.

Grade I: Microbubbles only in the ureter,

Grade II: Microbubbles in the renal pelvis; no significant renal pelvic dilation,

Grade III: Microbubbles in the renal pelvis + significant renal pelvic dilation + moderate calyceal dilatation,

Grade IV: Microbubbles in the renal pelvis + significant renal pelvic dilation + significant calyceal dilatation,

Grade V: Microbubbles in the renal pelvis + significant renal pelvic dilation and calyceal dilatation + loss of renal pelvis contour + dilated tortuous ureters.

Levovist (Levovist Schering, Berlin, Germany) was the first generation stabilized ultrasound contrast composed of palmitic-acid stabilized microbubbles to be utilized in ceVUS (28). It was first introduced for intravenous use in assessing cardiac shunts and defects in mid-1990s, and, later, approved for intravesical application. The Levovist bubble is a micro bubble of air—65% nitrogen and 35% oxygen— stabilized by palmitic acid. One gram of Levovist granules contains 999 mg D-galactose and 1 mg palmitic acid. The concentrations of microbubbles in freshly prepared batches (300 mg/ml) are within the range of approximately 1–2×108 microbubbles per millilitre of suspension (3). The Levovist suspension should always be freshly prepared prior to intravesical administration. The steps of preparation, as outlined by the manufacturer, must be strictly adhered to in order to avoid any reduction of contrast enhancement due to improper handling (29).

The administration of freshly prepared UCA has to be carried out within 30 min (30).

Some of the limitations of Levovist namely, low shelf life, early disintegration time and high quantity of dye required (,15,27,28,31) led to development and widespread use of second- generation contrast agent containing sulphur hexafluoride molecules (SonoVue®, Bracco, Milan, Italy) in VUS (27,28,31).

Currently, second-generation ultrasound contrast SonoVue (SonoVue, Bracco, Italy) has several intrinsic advantages over Levovist (32). SonoVue is a stabilized aqueous suspension of sulphur hexafluoride microbubbles with a phospholipid shell, which resonate by asymmetric contraction and expansion, and strongly increase the ultrasound backscatter allowing better visualization. It is not readily soluble in water, and, hence, remains stable for up to 6 hours compared with 2 h for the first-generation contrast (33).

Ultrasound contrast-enhanced voiding urosonography has become a routine diagnostic method for VUR in a number of European countries; however, it is not widely used in India. The aim of the present study was to analyze the clinical application and evaluate the safety of CeVUS as a diagnostic tool for VUR in children in order to establish a standardized operating procedure for CeVUS in paediatric VUR in our setup in India.

Need for the Study

Vesicoureteric reflux is an important association of paediatric urinary tract infection. Fluoroscopic micturating cystourethrography and radionuclide cystography have been quite an age-old techniques employed for detecting and grading vesicoureteric reflux. However, both modalities impose the risk of exposing the children to significant ionising radiation. Moreover, the detection rates drop down further due to intermittent fluoroscopic technique in micturating cystourethrography, and lower spatial resolution in radionuclide cystography. This led to development of an alternate newer radiation-free ultrasound-based contrast-enhanced voiding urosonography technique in Europe for 15 years.

This study was aimed to summarise the current literature and put forth our experience in our institution on detection of vesicoureteric reflux with this novel technique.

Aims and Objectives

Aim: To assess the efficacy and feasibility of ultrasound guided voiding cystourethrography as a standard investigating procedure for diagnosis of VUR in day-to- day practice.

Objectives: Comparison of ultrasound guided cystourethrography versus conventional voiding cystourethrography in terms of

Efficacy in diagnosis and follow-up of VUR

Practical feasibility

Safety and reliability # Cost effectiveness

Limitations

Materials and Methods

Design of the study: Cross sectional study.

Study duration: From January 2019 to December 2019 (1year).

Sampling frame: All the newly diagnosed and managed cases of vesicoureteric reflux under the age of 5 years by Department of Paediatric Urology in Bai Jerbai Wadia Hospital for Children, Mumbai were included.

Sample size: Since the total number of newly diagnosed cases of vesicoureteric reflux in children under the age of 5 years were only 30, they formed the sample size for the study.

Inclusion criteria

1. Newly diagnosed cases of vesicoureteric reflux with either modality from January to December 2019.
2. Children up to the age of 5 completed years and both sexes were included.

Exclusion criteria

1. Known or follow up cases of vesicoureteric reflux.
2. Children above 5 years of age.
3. Children with active UTI.

Method of collection of data

After obtaining clearance from the Institutional Ethical Committee and the informed consent from the study subjects in the regional language, the data was collected from the selected cases in a pre-designed and pre-tested semi- structured proforma with respect to the variables. All the data thus accured was systematically tabulated, collated and analysed.

Statistical Analysis: The data was entered in Excel Sheet. Descriptive statistics such as Mean, SD and percentage was used to present the data. The diagnostic accuracy of ce-VUS was evaluated by calculating sensitivity and specificity. Statistical difference between the techniques were performed by Chi square test or Fischer's exact test for small sample.

P value of <0.05 was considered as significant. Data analysis was performed by using SPSS v20.0 software.

Protocol employed during the study

A detailed history was obtained from the parents of every child in the study concerning antenatal and primary, current, and past medical problems. For each new patient, laboratory and imaging studies were performed as indicated namely

A) Hematological

Complete blood picture Renal function tests Serum electrolytes Blood gas analysis

B) Urine

Routine microscopy Urine Culture

C) Radiological

Ultrasonography of the kidneys, ureter and bladder (KUB).

For previously diagnosed patients, the previous medical records, laboratory data and imaging studies were reviewed. Routine urine analysis was performed anew on the day of the procedure in all cases to ensure absence of active UTI prior to the study.

Antibiotic prophylaxis was given to all patients before the procedure which consisted of Amoxicillin-Clavulinic acid, given at the dose of 50 mg/kg/day in two divided doses starting 5 days prior to the procedure. Prior to the actual procedure, all the children were evaluated thoroughly with USG KUB to assess the morphology of the kidneys, collecting systems and the bladder in supine, prone and lateral positions. Thereafter the children were catheterized using a 5Fr to 8Fr infant feeding tube (depending upon the age) and bladder was emptied. The children then underwent a conventional VCUG as the first procedure followed by ce-VUS on the same day. For the ce-VUS, Phillips Affinity 70G (Eindhoven, The Netherlands) ultrasound machine equipped with a C5-1MHz convex transducer was used. Specific contrast detection software with a mechanical index of 0.7 was used. All VUS studies were done by the same sonologist in the sonography department.

Procedure: Post catheterization and performing the conventional VCUG, the bladder was ensured to be empty and then refilled to the expected bladder capacity. The expected bladder capacity was calculated by standard method: Weight in kgs x 7 (for children under 2 years) and (Age in years + 2) x 30 – for children above 2 years of age.

There are two main methods for administering the contrast: one in which a dilution of contrast is prepared and then infused into the bladder and a second one in which the bladder is first filled with saline and afterwards contrast is injected directly into the full bladder. However, the chances of missing smaller grades of VUR are high in the second method due to non-uniform dilution of the contrast. This led us to use the first method in our study. In this technique, 0.5 ml to 1 ml of second generation UCA (Sonovue) was mixed with normal saline calculated as per bladder capacity and injected intravesically slowly under USG guidance. During this filling phase, the bladder, ureters, and kidneys are scanned to identify passive reflux. Once the bladder was filled completely or once the child had a desire to urinate, filling was stopped, urinary catheter removed and child was allowed to void. During voiding, the bladder, ureters and the kidneys were imaged alternatively similar to pre contrast evaluation to identify active reflux. Reflux was said to be present when echogenic microbubbles appeared in the ureter or renal pelvis.

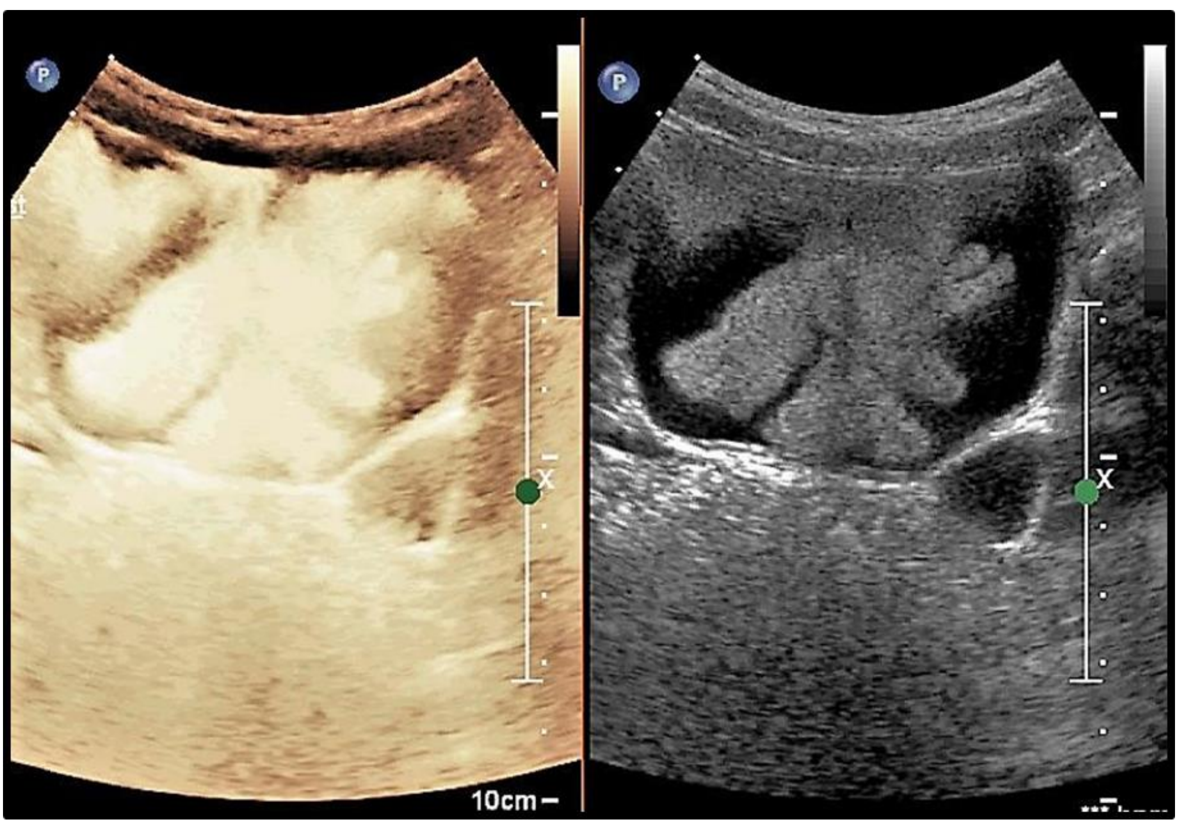

Fig 1: Early filling phase demonstrating Ultrasound contrast agent being instilled into the bladder (note dilated left ureter). A) Grey scale with Contrast mode. B) Grey scale mode alone.

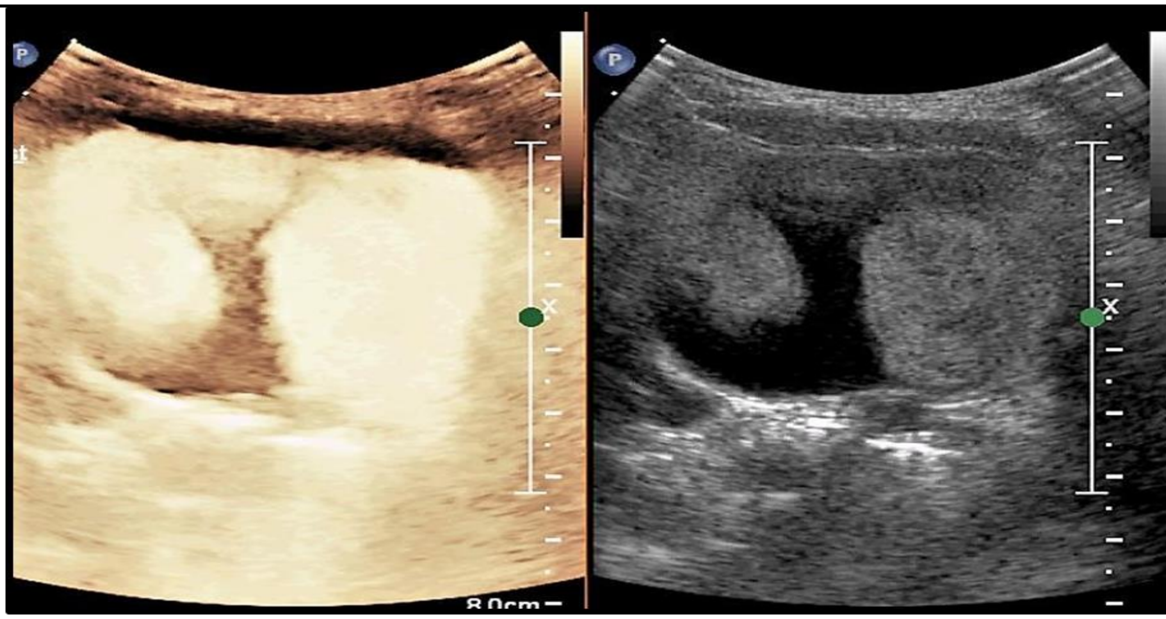

Fig 2: “Grey scale with Contrast mode” and “Grey scale” showing intra vesical US contrast agent during the filling phase in a case of right complete duplex system.

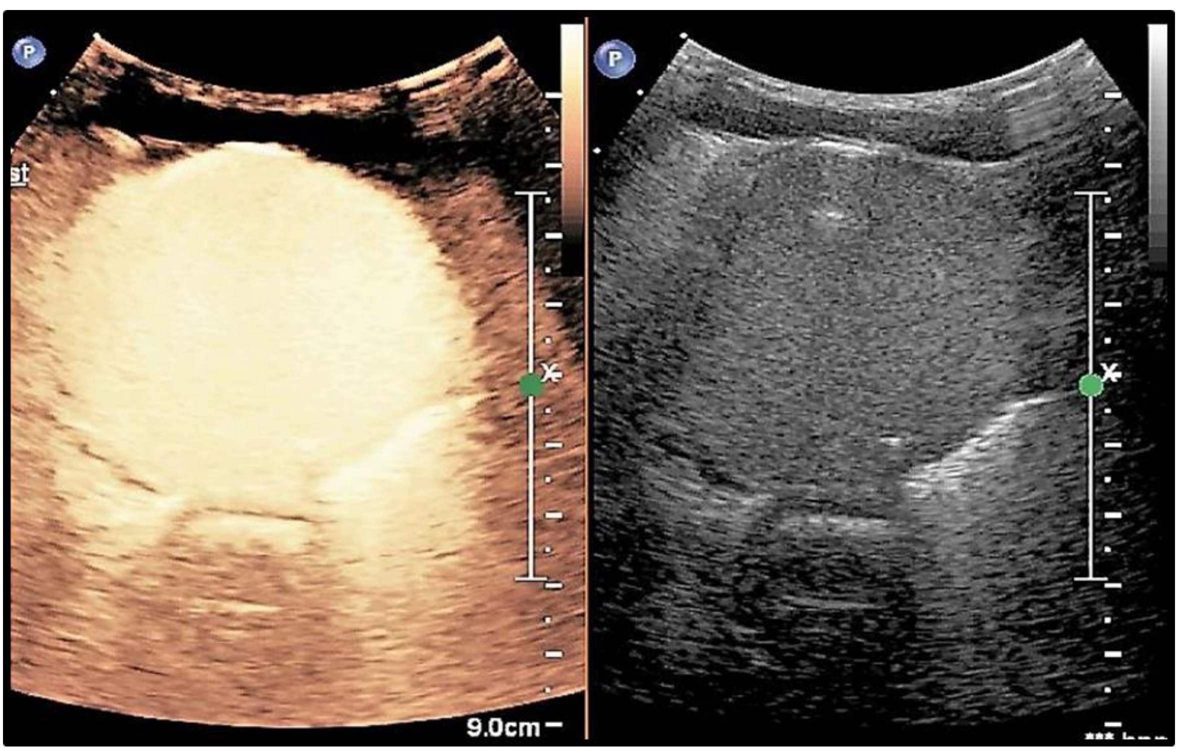

Fig 3: Full bladder image. Normal study showing bladder filled with US contrast agent with non-visualized ureters on either side.

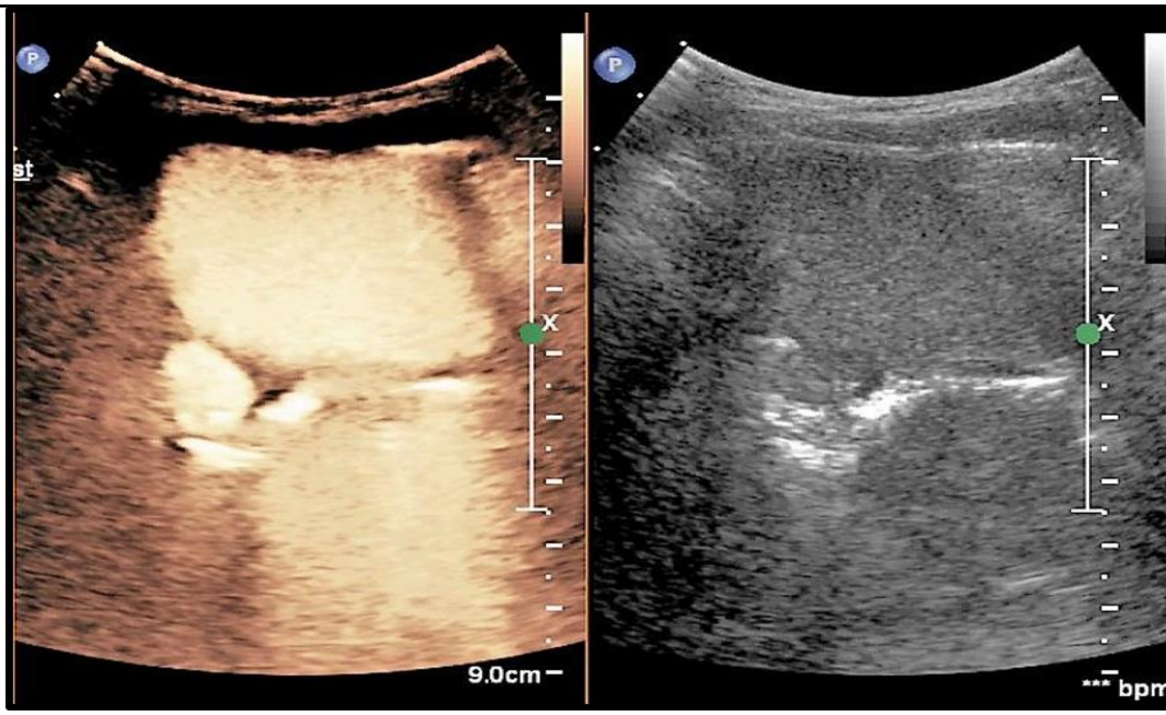

Fig 4: Full bladder depicting dilated refluxing right ureter in a case of right solitary kidney.

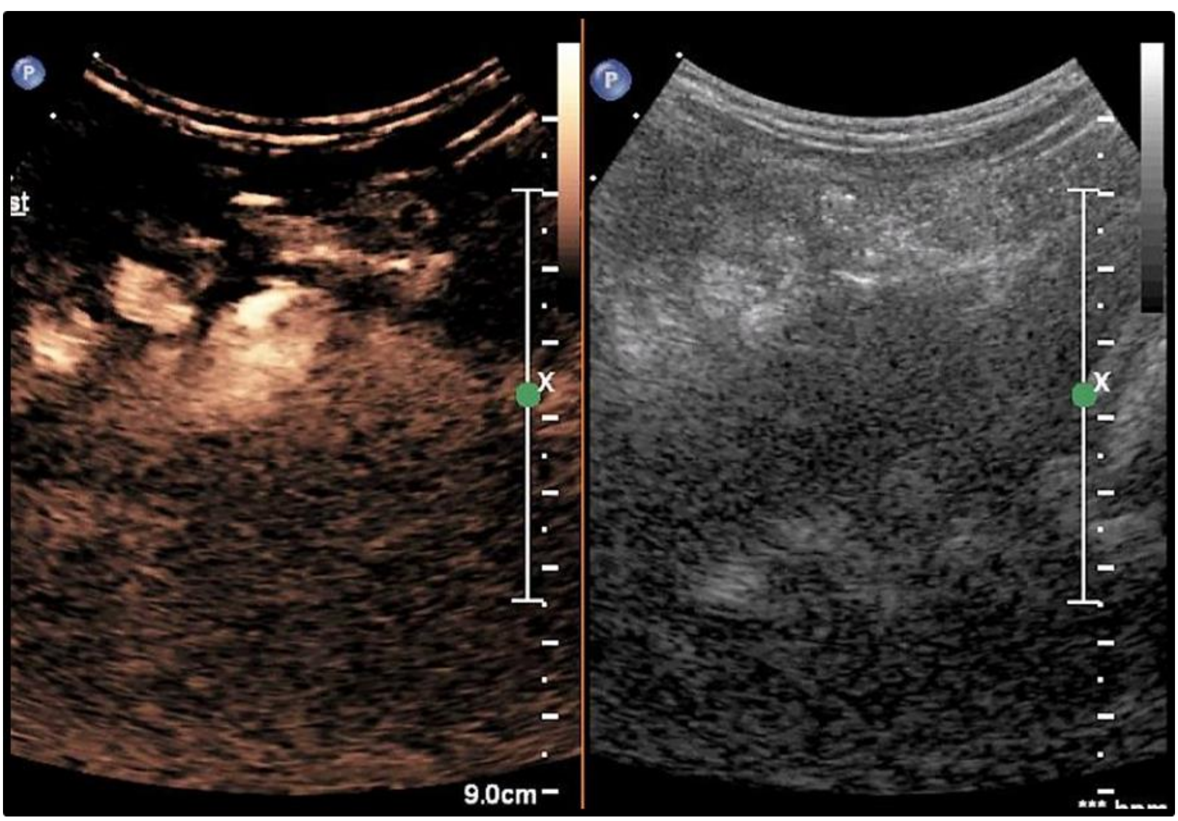

Fig 5: Grade V VUR as seen in “Grey scale with Contrast” mode and “Grey scale” mode alone.

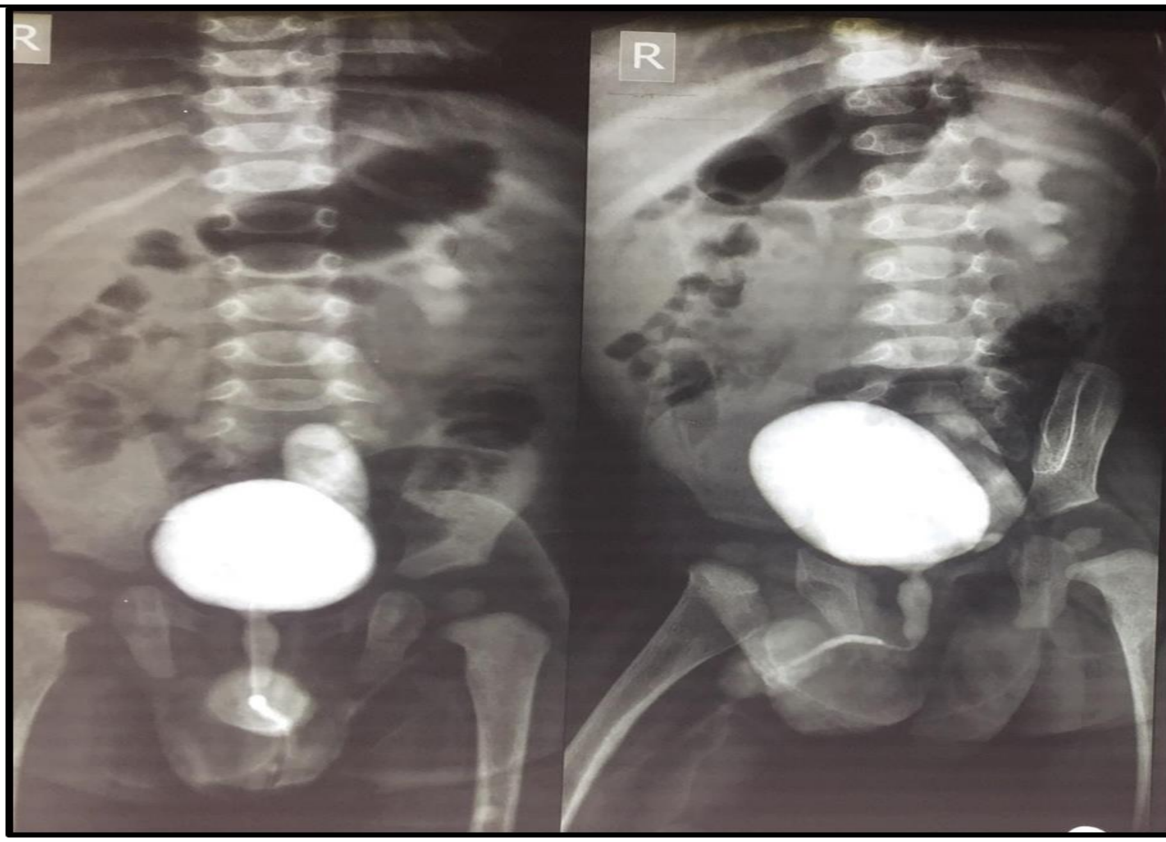

Fig 6.1: Conventional VCUG in a case of PUV with Left grade III VUR.

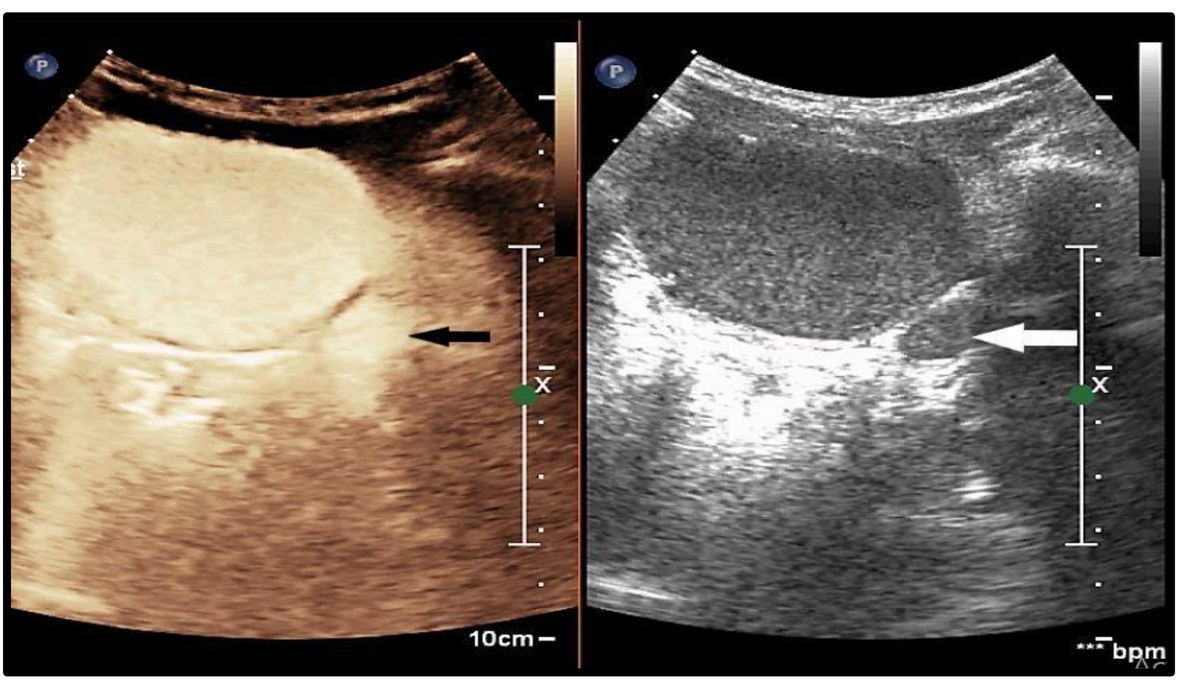

Fig 6.2: Dilated refluxing left ureter in the same case being depicted in “Grey scale with Contrast mode”

(black arrow).“Grey scale” mode alone does show the dilated ureter (white arrow); however identification of reflux does need a dedicated contrast mode.

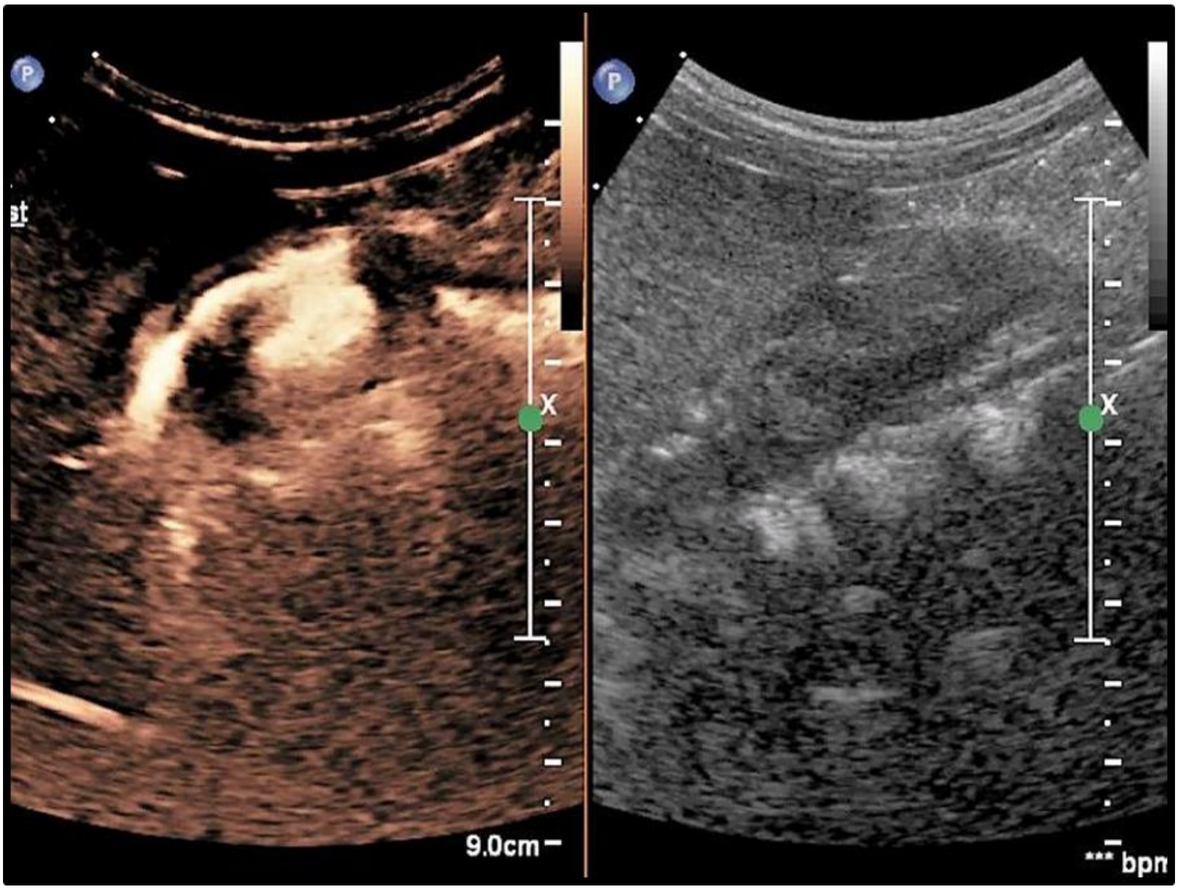

Fig 6.3: Renal imaging in the same patient revealing grade III VUR.

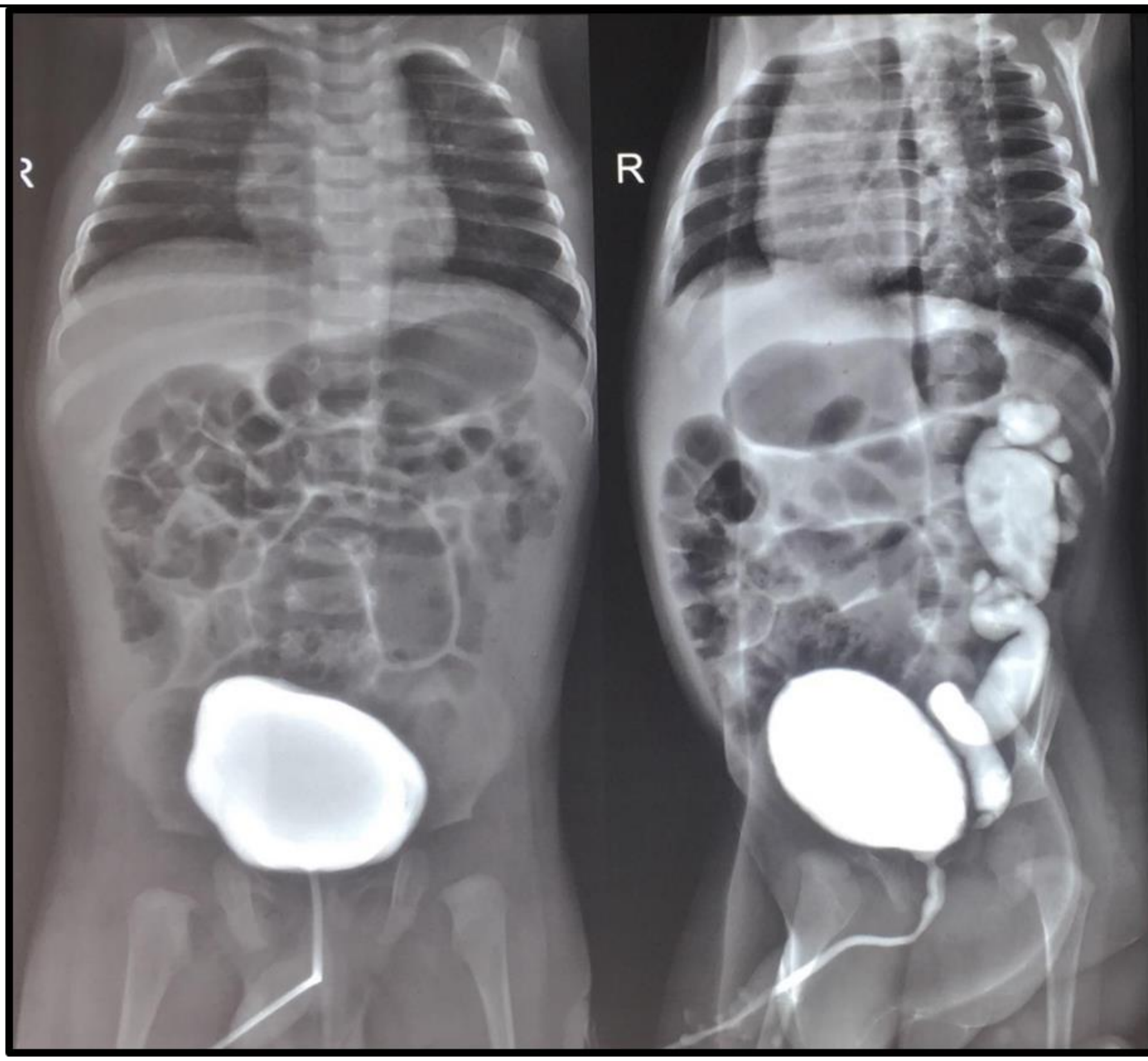

Fig 7.1: Conventional VCUG image of a case of Left Primary Grade V VUR.

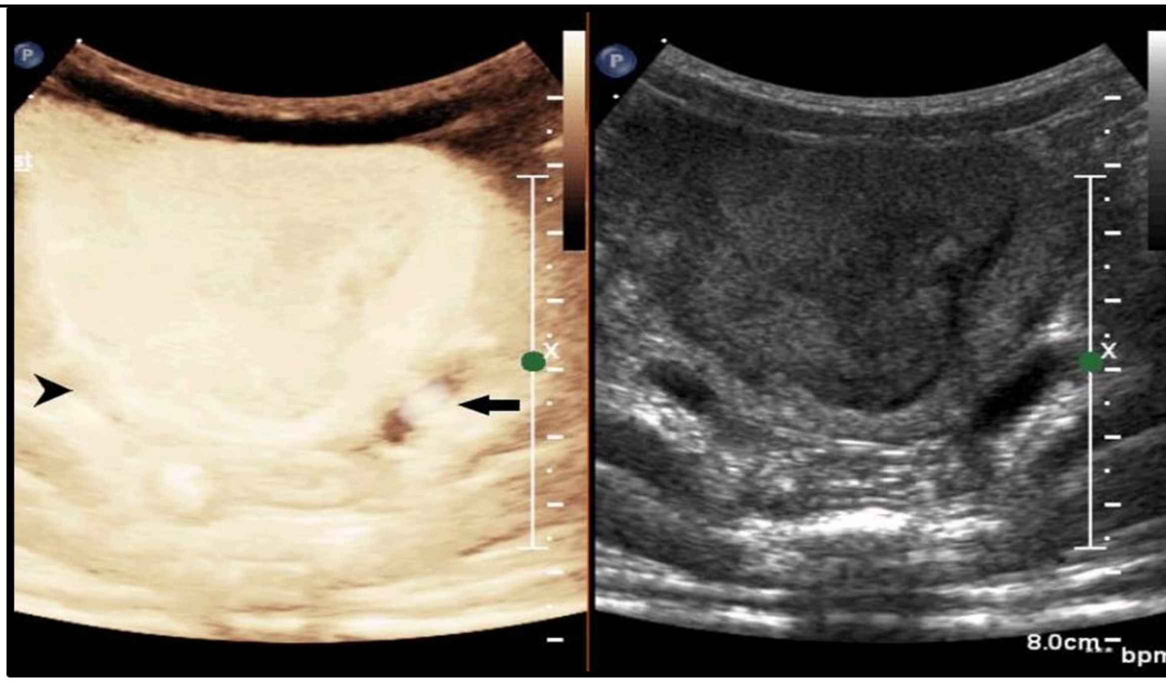

Fig 7.2: ce-VUS imaging of the same case showing appearance of echogenic bubbles in bilateral ureteric orifices, against left side only on conventional VCUG.

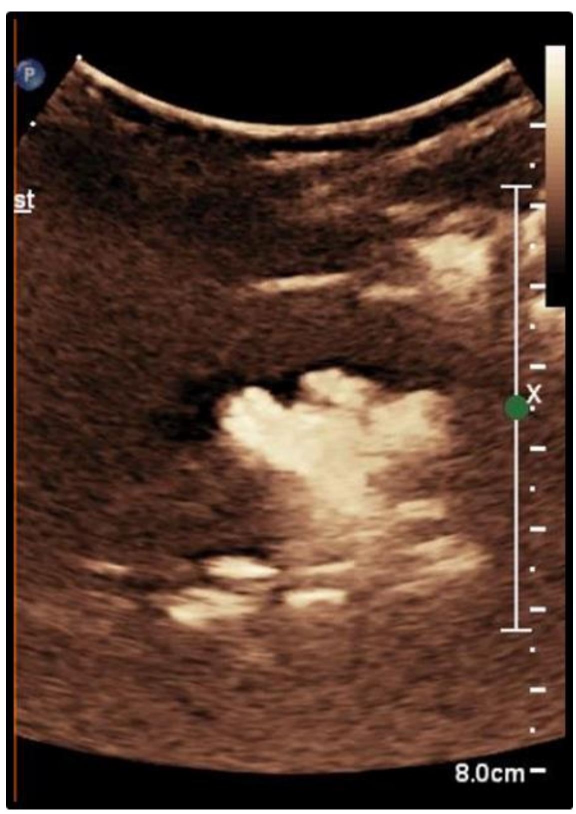

Fig 7.3: Right grade III VUR in same case.

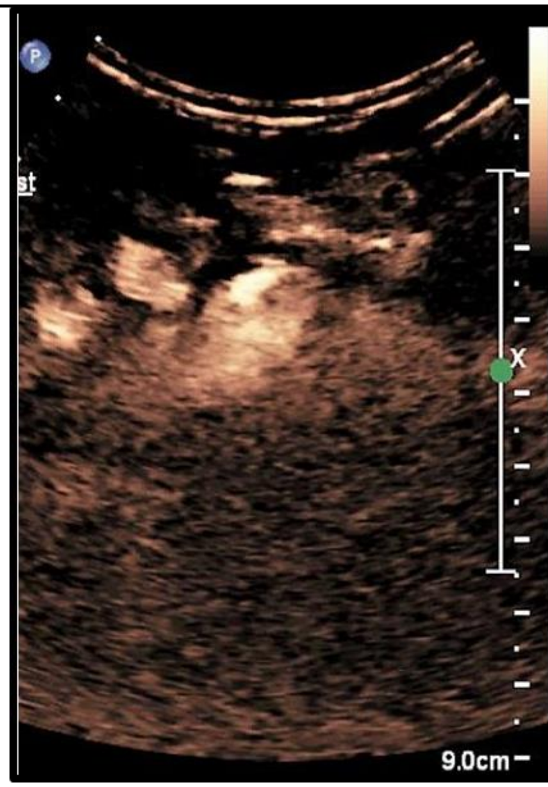

Fig 7.4: Left grade V VUR in same case on ce-VUS

Fig 8.1: Filling phase on ce-VUS in case of right complete duplex system. Upper moiety ureter marked with arrow, lower moiety ureter marked with arrow head.

Fig 8.2: First appearance of reflux in both moiety ureters on ce-VUS.

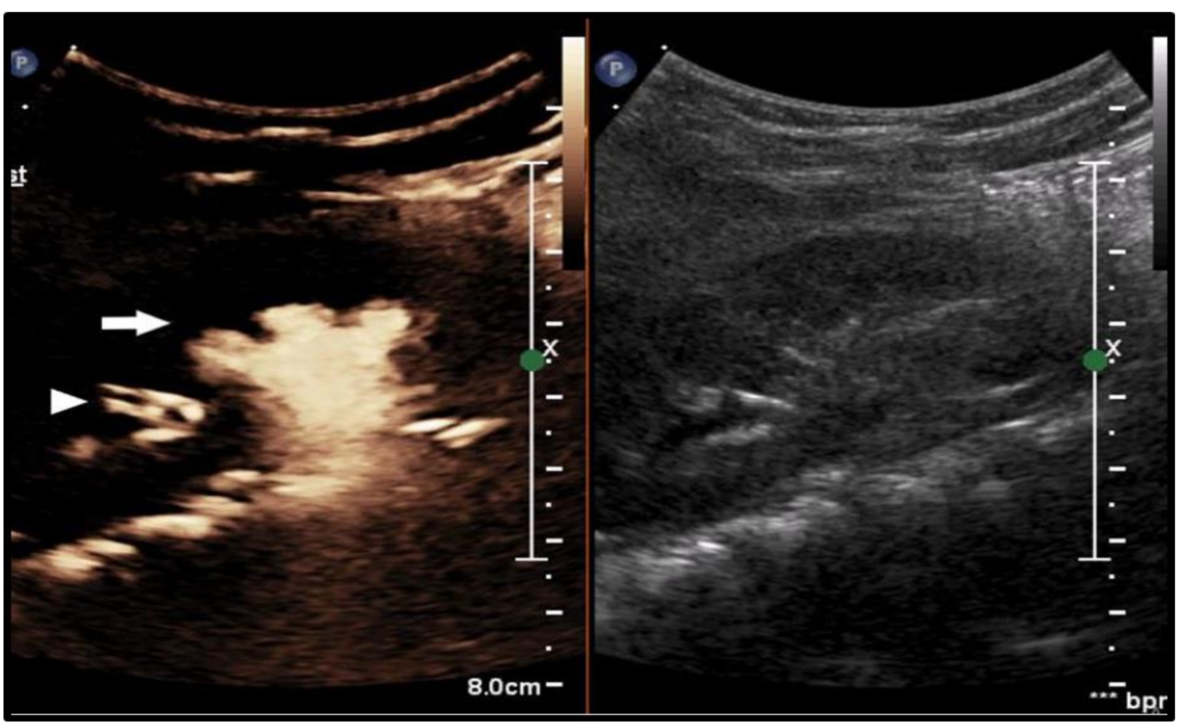

Fig 8.3: Renal imaging in the same case showing reflux in both moieties of duplex system as marked with arrow (lower moiety) and arrow head (upper moiety).

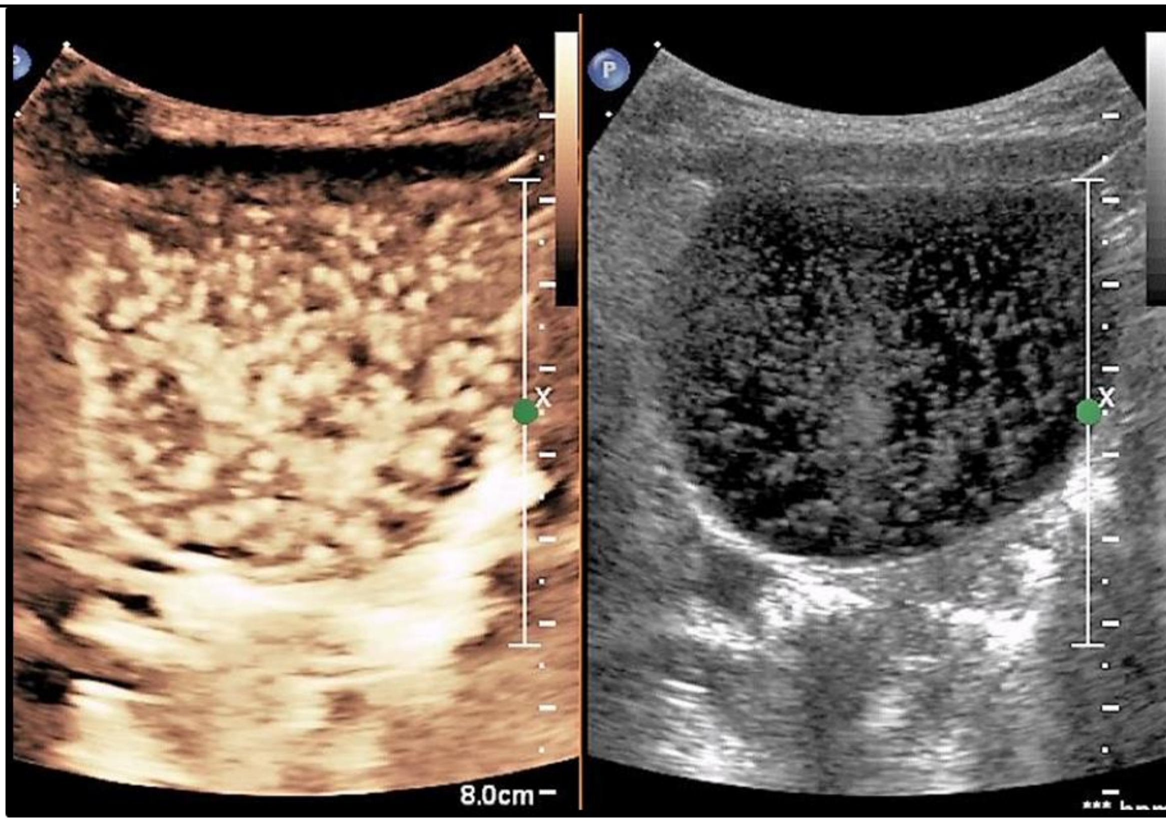

Fig 9: Pitfall: ce-VUS imaging demonstrating non uniform distribution of the echo contrast secondary to faulty techniques of contrast administration or premature disintegration.

Results

Demographics

A total no 30 children were enrolled in the study ranging from 18 days to 5 completed years with a mean age of 2 years 12 days. There were 19 males and 11 females with a male:female ratio of 1.72:1.

Details of sex and age wise distribution has been shown below.

Table 1: Sex wise distribution of patients

Males	**Females**	**Total**
19	11	30

Table 2: Age wise distribution of patients

Age	Number	Percentage
0-6 months	8	26.66
6 months-1 year	5	16.67
1-2 years	3	10.00
2-3 years	5	16.67
3-4 years	5	16.67
4-5 years	4	13.33

Laterality of the systems involved

Of the 30 children involved in the study, unilateral VUR was noted in 21 cases (21 refluxing units) and bilateral in 09 (18 refluxing units) cases thus amounting to a total of 39 refluxing units. Among the unilateral cases, left side was found to be more commonly involved.

The detailed distribution is as under (Table 2).

Table 3: Laterality of the systems involved

Laterality	Unilateral		Bilateral	Total
Number	21 (21 units)		09 (18 units)	30 (39 units)
Side	Right	Left		
	09/21	12/21		
Percentage	42.85	57.15		
	70		30	100

Among the studied 30 cases, VUR was associated with PUV in 12 (40%) cases and Neurogenic bladder in 2 (6.66%) cases, rest 16 (53.34%) were primary VUR.

Table 4: Associated pathologies

Pathology	PUV			Neurogenic bladder
Cases	12/30 (40%)			02/30 (6.66%)
	Unilateral		Bilateral	
	Right	Left		

	03/12	05/12	04/12	
Percentage	25	41.67	33.33	

Clinical presentation

The most common mode of diagnosis was secondary to antenatal presentation, seen in 13 cases (43.33%), followed by recurrent UTI's in 8 cases (26.66%).

Dribbling micturition was seen in 5 cases (16.66%).

Bowel bladder dysfunction was noted in 4 cases (13.33%).

Table 5: Clinical presentation

Presentation	Antenatal diagnosis	Recurrent UTI's	Dribbling micturition	Bowel bladder dysfunction
Cases	13	08	05	04
Percentage	43.33	26.66	16.66	13.33

Efficacy

Out of the 30 cases (39 refluxing units) studied, 3 cases: 2 unilateral (2 refluxing units) and 1 refluxing unit in a bilateral VUR (2 refluxing units), were picked up only on conventional MCU and missed on ce-VUS. Thus 03/39 (07.69%) refluxing units were diagnosed only on conventional MCU.

One case of unilateral VUR (1 refluxing unit) was diagnosed on ce-VUS and missed on conventional MCU. Thus 01/39 (02.56%) refluxing units was picked up by ce-VUS alone.

The remainder of 35 refluxing units were diagnosed both conventional and ce-VUS together.

Using MCU as the reference method, the sensitivity of ceVUS was 97.22% (CI: 85.47% to 99.9.%), and diagnostic accuracy was found to be 89.74% (CI: 75.78% to 97.13%). Approximately 7.69% of all reflux units were diagnosed by MCU alone, and 2.56% were diagnosed by ceVUS alone. However, the refluxing units missed on ceVUS were of low grade, while the one missed on MCU were of medium-to-high grade. The intermittent nature of vesicoureteric reflux, together with intermittent fluoroscopy, and dilution of radiographic contrast were postulated to result in lower detection rate of high-grade reflux on MCU. On the other hand, the lower detection rate of low-grade reflux on ceVUS is attributed to the difficulty in visualising retrovesical regions and non-dilated by the intravesical contrast.

Safety

ce-VUS involves intravesical instillation of ultrasound contrast under continuous sonographic examination. Since the contrast agent is not administered intravenously systemic complications are extremely rare. An European territory-wide questionnaire based survey revealed that (38), there were no allergic reactions or systemic complications related to SonoVue in 5079 paediatric ce-VUS examinations performed in 45 European centres. However, a few minor complications related to catheterization did occur.

Our study also confirmed the safety profile of ce-VUS. No complications related to the contrast agent, were noticed (40).

The major advantage of using ce-VUS is its lack of ionizing radiation. In a recent study on radiation dose of paediatric VCUG by Sulieman et al.(41), the mean entrance surface dose for VCUG with positive reflux was 1.45 mGy, and negative reflux was 1.05 mGy. As gonads were inside the radiation field during the examination, there was a higher organ equivalent dose to ovaries (0.44 mSv) and testes (0.33 mSv) than to thyroid (0.006 mSv).[29] The estimated risks of malignancy of ovaries and testes were 4.4 x 10-7 and 3.3 x 10-7, respectively(41).

Considering that many of these children are likely to undergo more than one VCUG in their entire lifetime, in addition to other imaging modalities using ionizing radiation, it becomes even more imperative to consider imaging modalities with no radiation exposure such as ce-VUS.

Feasibility

ce-VUS though a novel technique, is technically analogous with MCU, except that it involves sonographic examination of the urinary tract instead of fluoroscopy. In terms of manpower too, the number involved is similar in both the techniques. Moreover, the dosage of SonoVue required in each ceVUS examination ranged from 0.5 mL to 1 mL, which is adequate for at least three cycles of filling and voiding phases. Thus, in our study, one vial of SonoVue could be shared among several patients in each session, allowing effective usage of the contrast agent(40).

Cost effectiveness

The conventional VCUG entails the use of more widely and readily available water- soluble contrast - 76% Urograffin which, not only is widely but also is readily available and at a much affordable price. One 20 ml vial of 76% Urograffin costs around 20 rupees per patient as one vial would usually be sufficient for a child under the age of 5 years.

On the other hand, one vial of ultrasound contrast agent costs 5,000 rupees approximately. Since it can be used as a multi-dose vial and can be shared among 10 patients at least, the effective cost of the contrast per child was 500 rupees.

Despite variations in the price of both the contrast agents, the advantages ce-VUS offers over VCUG is noteworthy.

Limitations

It is known that the acoustic shadowing produced by the high concentration of ultrasound contrast can obscure the retrovesical region and, thus, decrease the sensitivity of ce-VUS in detecting grade I reflux(42). Though a drawback, this can easily be remedied by dilution of ultrasound contrast by continuous saline infusion and is best assessed during the second cyclical examination(40).

A major limitation in employing this novel technique in day-to-day practice is its learning curve. There is a considerable technical learning curve in the identification of the optimal concentration of the contrast, position, and ultrasound settings for ideal visualization of VUR.

Another limitation in employing ce-VUS compared to its fellow techniques is failure to simultaneously evaluate the urethra in the same sitting as that of ureters and the kidneys, thus warranting a cyclical or an additional round of entire procedure subjecting to added risk of UTI secondary to repeated catheterization.

Besides, ce-VUS has limitation in those examinations that require detailed anatomical assessment, such as in evaluation of recto-urethral fistula in distal loopogram in neonates with anorectal malformation(40). However, the majority of indications of MCU, can also be performed by ceVUS.

Discussion

Currently different imaging modalities are available for diagnosing VUR which include VCUG, radio nuclide cystogram (RNC), and ce-VUS. VCUG has significant ionizing radiation due to the use of intermittent screening. RNC although highly sensitive, with less radiation exposure, lacks the anatomic resolution of VCUG.

ce-VUS, introduced in the early 1990s was originally thought to be a promising alternative method for classical VCUG. The short half-life and quite fast contrast destruction substantially limited the use of this method. However, the methodology of ce- VUS has changed over the last decade, especially due to the second-generation contrast agents now used for examination. Indeed, the second-generation UCAs have been recently

introduced for common clinical use, replacing the older contrast agents including Levovist (Bayer-Schering Pharma, Berlin, Germany) which was commonly used in ce-VUS, but has been recently withdrawn from the market by the producer. In comparison to the second generation UCAs, the first UCA generation was not durable, and the results were highly dependent on the agent's concentration level in the bladder(23). There are two major limitations of the use of second-generation UCAs in paediatric population, namely off-label use in the population, and the limited number of studies evaluating the sensitivity and specificity of this method (43-47). According to the European Society of Paediatric Radiology (ESPR), standard VCUG should be performed under fluoroscopic guidance enhanced with several spot films(48). The examination results in effective radiation dosage of around 0.5–
0.8 mSv. In our study found no significant difference in sensitivity between ce-VUS and VCUG, suggesting that both methods can be alternatively used with some reservations (Fig. 1, Fig. 2). In some cases, we noticed a quick destruction of UCA due to increased intravesical pressure in children who did not cooperate and were crying. Some children had problems with postponed voiding phase, which excluded the possibility of ce-VUS use in these cases, while VCUG could still be performed. These specific UCA characteristics minimize the usefulness of this method for evaluation of the urethra during voiding, predominantly in children who are unable to cooperate.

The main advantage of ce-VUS over the other two is the fact that it does not expose the child to ionizing radiation. Furthermore, ce-VUS is a real time imaging compared to VCUG, which often gives only a snapshot of the procedure. Kis et al. reported ce-VUS to be more sensitive than VCUG since it has the potential to detect intermittent VUR(49). It also can be repeated without exposure to radiation in case of failed procedure. One disadvantage of ce-VUS is limited visualization of urethra, although others have suggested that adequate imaging of urethra is possible with VUS(27,45,47,49,50). Sulphur hexafluoride (SonoVue) can be injected as an intravenous contrast agent also to identify enhancement on ultrasound in vascular lesions. It is excreted by lungs and has a good safety profile(51). The contrast agent has a good shelf life of 6-12 hours after reconstitution. For VUS, 0.5 to 1ml ml with appropriate volume of normal saline is used to fill bladder. As it comes as 5 ml pack, it can be used for up to ten children, thereby reducing the cost.

Like VCUG and direct RNC, it is still necessary to catheterize the bladder ce-VUS for VUS. This is a major drawback of all direct reflux examinations and one that makes them invasive. Attempts to generate bubbles exogenously using high-intensity focused US would solve this problem but have not yet moved beyond the stage of animal studies(52).

Conclusion

It is important to realize that a breakthrough to implement US for reflux diagnosis, which had begun in the late 1970s, only came with the availability of a stable UCA. Advances in US technology resulting in marked improvement in the depiction of microbubbles have facilitated many procedural aspects in addition to the diagnostic accuracy of the modality.

Contrast-enhanced voiding urosonography using intravesical ultrasound contrast agent should be introduced as a valid alternative diagnostic modality for detecting vesicoureteric reflux, based on its radiation-free, highly efficacious, reliable, and safe characteristics(53); MCU can be reserved for patients requiring detailed anatomical assessment.

With no radiation exposure, it may also become an acceptable tool to screen siblings of children with VUR.

In summary, the present study supports the safety and efficacy of CeVUS as an innoxious and sensitive tool for diagnosis, follow up and screening VUR in high-risk children.

In conclusion, in an era of heightened radiation awareness and protection, radiation doses to infants and children should be kept as low as reasonably achievable. With improved operator learning curve for ce-VUS, it has the potential to replace VCUG. The longer dynamic imaging acquisition of ce-VUS also suits the intermittent nature of VUR. ce-VUS using second-generation contrast agent may be introduced as a valid alternative diagnostic modality for detecting VUR, based on its radiation free, highly efficacious, reliable, and safe characteristics(45,54).

References

1. 1. Levitt SB, and Weiss RA: Vesicoureteral reflux: natural history, classification and reflux nephropathy, in Kelalis PP, King LR, and Belman AB (Eds): Clinical Pediatric Urology. Philadelphia, WB Saunders, 1985, vol I, pp 355–380.

2. Darge K (2002) Diagnosis of vesicoureteral reflux with ultrasound. Pediatr Nephrol 17:52–60.

3. Voiding urosonography with ultrasound contrast agents for the diagnosis of vesicoureteric reflux in children... Kassa Darge.

4. Kaneko K, Kuwatsuru R, Fukuda Y et al (1994) Contrast sonography for detection of vesicoureteral reflux. Lancet 344:687.

5. Von Rohden L, Bosse U, Wiemann D (1995) Refluxsonographie bei Kindern mit einem

Ultraschallkontrastmittel im Vergleich zur Röntgenmiktionszystourethro-graphie. Paediat Prax 49:49–58.

6. McEwing RL,Anderson NG, Hellewell S et al (2002) Comparison of echo-enhanced ultrasound with fluoroscopic MCU for the detection of vesicoureteral reflux in neonates. Pediatr Radiol 32:853–858.

7. Mentzel HJ, Vogt S, Patzer L et al (1999) Contrast-enhanced sonography of vesicoureterorenal reflux in children: preliminary results. AJR 173:737–740.

8. Vassiou K, Vlychou M, Moisidou R et al (2004) Contrast-enhanced sonographic detection of vesicoureteral reflux in children: Comparison with voiding cystourethrography. Rofo 176:1453–1457.

9. Radmayr C, Klauser A, Pallwein L et al (2002) Contrast enhanced reflux sonography in children: a comparison to standard radiological imaging. J Urol 167:1428–1430.

10. Elias P, Rejtar P, Sylva S et al (1999) Preliminary experience with contrast-enhanced ultrasound cystography in the diagnosis of vesicoureteral reflux. Ces Radiol 53(Suppl 1):4– 8.

11. Escape I, Martinez J, Bastart F et al (2001) Usefulness of echocystography in the study of vesicoureteral reflux. J Ultrasound Med 20:145–149.

12. Farina R, Arena C, Pennisi F et al (1999) Retrograde cystography US: a new ultrasound technique for the diagnosis and staging of vesicoureteral reflux. Radiol Med 97:360–364.

13. Ascenti G, Chimenz R, Zimbaro G et al (2000) Potential role of colour-Doppler cystosonography with echocontrast in the screening and follow-up of vesicoureteral reflux. Acta Paediatr 89:1336–1339.

14. Berrocal T, Gaya F, Arjonilla A et al (2001) Vesicoureteral reflux: diagnosis and grading with echo-enhanced cystosonography versus voiding cystourethrography. Radiology 221:359–365.

15. Bosio M (1998) Cystosonography with echocontrast: a new imaging modality to detect vesicoureteric reflux in children.Pediatr Radiol 28:250–255.

16. Piaggio G, Degl' Innocenti ML, Toma P et al (2003) Cystosonography and voiding cystourethrography in the diagnosis of vesicoureteral reflux. Pediatr Nephrol 18:18–22.

17. Riccabona M, Mache CJ, Lindbichler F (2003) Echo-enhanced color Doppler cystosonography of vesicoureteral reflux in children:improvement by stimulated acoustic emission. Acta Radiol 44:18–23.

18. Xhepa R, Bosio M, Manzoni G (2004) Voiding cystourethrosonography for the diagnosis of vesicoureteral reflux in a developing country. Pediatr Nephrol 19:638–643.

19. Darge K, Zieger B, Rohrschneider W et al (2001) Contrastenhanced harmonic imaging for the diagnosis of vesicoureteral reflux. AJR 177:1411–1415.

20. Kopitzko A, Cornely D, Reither K et al (2004) Low contrast dose voiding urosonography in children with phase inversion imaging. Eur Radiol 14:2290–2296.

21. Maté A, Bargiela A, Mosteiro S et al (2003) Contrast ultrasound of the urethra in children. Eur Radiol 13:1534–1537.

22. Mentzel HJ, Vogt S, Joan U et al (2002) Voiding urosonography with ultrasonography contrast medium in children. Pediatr Nephrol 17:272–276.

23. Nakamura M, Shinozaki T, Taniguchi N et al (2003) Simultaneous voiding cystourethrography and voiding urosonography reveals utility of sonographic diagnosis of vesicoureteral reflux in children. Acta Paediatr 92:1422–1426.

24. Uhl M, Kromeier J, Zimmerhackl LB et al (2003) Simultaneous voiding cystourethrography and voiding urosonography. Acta Radiol 44:265–268.

25. Kopac M, Kenig A, Kljucevsek D et al (2005) Indirect voiding urosonography for detecting vesicoureteral reflux in children.Pediatr Nephrol 20:1285–1287.

26. Atala A, Wible JH, Share JC, Carr MC, Retik AB, Mandell J. Sonography with sonicated albumin in the detection of vesicoureteral reflux. J Urol 1993;150:756-8.

27. Darge K, Troeger J. Vesicoureteral reflux grading in contrast-enhanced voiding urosonography. Eur J Radiol 2002;43:122-8.

28. Fritzsch T, Schlief R. Levovist. Drugs Fut 1995;20:1224-7.

29. Darge K, Troeger J, Duetting T et al (1999) Reflux in young patients: comparison of voiding US of the bladder and retrovesical space with echo enhancement versus voiding cystourethrography for diagnosis. Radiology 210:201–207.

30. Albrecht T, Blomley M, Bolondi L et al (2004) Guidelines for the use of contrast agents in ultrasound. January 2004. Ultraschall Med 25:249–256.

31. Tse KS, Wong LS, Lau HY, Fok WS, Chan YH, Tang KW, et al. Pediatric vesicoureteral reflux imaging: where are we? Novel ultrasound-based voiding urosonography. Hong Kong Med J 2014;20:437-43.

32. Schneider M. SonoVue, a new ultrasound contrast agent. Eur Radiol 1999;9 Suppl 3:347S-348S.

33. Rossling G. Physico-chemical properties of Levovist. Proceedings of the 2nd European Meeting on Sonographic Diagnosis.

34. Hanbury DC, Coulden RA, Farman P, Sherwood T. Ultrasound cystography in the diagnosis of vesicoureteric reflux. Br J Urol 1990 Mar;65(3):250e3.

35. Atala A, Ellsworth P, Share J, Paltiel H, Walker RD, Retik AB. Comparison of sonicated albumin enhanced sonography to fluoroscopic and radionuclide voiding cystography for detecting vesicoureteral reflux. J Urol 1998 Nov;160(5):1820e2.

36. Kaneko K, Kuwatsuru R, Fukuda Y, Yamataka A, Yabuta K, Katayama H, et al. Contrast sonography for detection of vesicoureteral reflux. Lancet 1994 Sep 3;344(8923):687.

37. Back SJ, Maya C, Darge K, Acharya PT, Barnewolt CE, Coleman JL, et al. Pediatric contrast-enhanced ultrasound in the United States: a survey by the contrast-enhanced ultrasound task force of the society for pediatric radiology. Pediatr Radiol 2018 Feb 13. https://doi.org/10.1007/s00247-018-4088-x.

38. Riccabona M. Application of a second-generation US contrast agent in infants and children–a European questionnaire-based survey. Pediatr Radiol 2012 Dec;42(12):1471-80. https://doi.org/10.1007/s00247-012-2472-5.

39. Saltychev M, Ristola MT, Laimi K, Hurme T. Accuracy of ultrasonography in predicting vesicoureteral reflux in children: a meta-analysis. Scand J Urol 2016 Aug;50(4):239e45. https: //doi.org/10.1080/21681805.2016.1194462.

40. Tse KS, Wong LS, Fan TW, et al. New radiation-free era in reflux imaging for paediatric urinary tract infection (UTI): voiding urosonography with intravesical ultrasound contrast—first local pilot study. Paper presented at 2013 Hospital Authority Convention; 2013 May 15-16; Hong Kong.

41. Sulieman A, Theodorou K, Vlychou M, Topaltzikis T, Kanavou D, Fezoulidis I, et al.
Radiation dose measurement and risk estimation for pediatric patients undergoing micturating cystourethrography. Br J Radiol 2007;80:731-7.

42. Darge K. Voiding urosonography with US contrast agents for the diagnosis of vesicoureteric reflux in children. II. Comparison with radiological examinations. Pediatr Radiol 2008;38:54-63; quiz 126-7.

43. Duran C, del Riego J, Riera L, Martin C, Serrano C, Palaña P: Voiding urosonography including urethrosonography: high-quality examinations with an optimised procedure using a second-generation US contrast agent. Pediatr Radiol 2012; 42: 660–667.

44. Ascenti G, Zimbaro G, Mazziotti S, Chimenz R, Fede C, Visalli C et al.: Harmonic US imaging of vesicoureteric reflux in children: usefulness of a second generation US contrast agent. Pediatr Radiol 2004; 34: 481–487.

45. Papadopoulou F, Anthopoulou A, Siomou E, Efremidis S, Tsamboulas C, Darge K: Harmonic voiding urosonography with a second-generation contrast agent for the diagnosis of vesicoureteral reflux. Pediatr Radiol 2009; 39: 239–244.

46. Papadopoulou F, Ntoulia A, Siomou E, Darge K: Contrast-enhanced voiding urosonography with intravesical administration of a second-generation ultrasound contrast agent for diagnosis of vesicoureteral reflux: prospective evaluation of contrast safety in 1,010 children. Pediatr Radiol 2014; 44: 719–728.

47. Darge K: Voiding urosonography with US contrast agent for the diagnosis of vesicoureteric reflux in children: an update. Pediatr Radiol 2010; 40: 956–962.

48. Riccabona M, Avni FE, Blickman JG, Dacher JN, Darge K, Lobo ML et al.: Imaging recommendations in paediatric uroradiology: minutes of the ESPR workgroup session on urinary tract infection, fetal hydronephrosis, urinary tract ultrasonography and voiding cystourethrography, Barcelona, Spain, June 2007. Pediatr Radiol 2008; 38: 138–145.

49. Kis E, Nyitrai A, Várkonyi I, Máttyus I, Cseprekál O, Reusz G, et al. Voiding urosonography with second-generation contrast agent versus voiding cystourethrography. Pediatr Nephrol 2010;25:2289-93.

50. Novljan G, Kenig A, Rus R, Kenda RB. Cyclic voiding urosonography in detecting vesicoureteral reflux in children. Pediatr Nephrol 2003;18:992-5.

51. Bokor D, Chambers JB, Rees PJ, Mant TG, Luzzani F, Spinazzi A. Clinical safety of SonoVue, a new contrast agent for ultrasound imaging, in healthy volunteers and in patients with chronic obstructive pulmonary disease. Invest Radiol 2001;36:104-9.

52. Fowlkes JB, Carson PL, Chiang EH et al (1991) Acoustic generation of bubbles in excised canine urinary bladder. J Acoust Soc Am 89:2740–2744.

53. Wong LS, Tse KS, Fan TW, et al. Voiding urosonography with second-generation ultrasound contrast versus micturating cystourethrography in the diagnosis of vesicoureteric reflux. Eur J Pediatr 2014 Mar 23. Epub ahead of print.

54. Tse KS, Wong LS, Lau HY, Fok WS, Chan YH, Tang KW, et al. Pediatric vesicoureteral reflux imaging: where are we? Novel ultrasound-based voiding urosonography. Hong Kong Med J 2014;20:437-43.

Medtronic