# Haematuria in rabbits: detecting symptoms as true or false

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**ELISABETTA MANCINELLI** DVM, CertZooMed, DipECZM(Small Mammal), MRCVS discusses diagnostic methods to identify whether a rabbit's presenting signs are truly haematuria or just pigmentation of urine, as well as causal factors

**VETERINARY care of small exotic mammals is an ever-growing component in the field of zoological medicine. There is a vast amount of medical information about rabbits, often originating from the laboratory setting.**

However, the rabbit is now the most popular exotic animal patient in many practices, and many owners are dedicated to excellent health care for their pets. It is of utmost importance to be able to provide these animals with the same level of care as other more common mammal species (such as dogs and cats) and give them the attention they deserve.

Veterinarians must be aware of a rabbit's anatomical and physiological parameters, so when a patient is presented for illness or to have a surgical procedure performed, the special needs of these animals are met. This eventually results in improved medical care for this species and, ultimately, in a longer and healthier lifespan.

Haematuria is a commonly encountered clinical sign in pet rabbits and this article will focus on some of the most common causes encountered in clinical practice.

## Detection importance

Macroscopic haematuria is grossly visible in the urine (Figure 1), while microscopic haematuria is not

apparent with the naked eye. Persistent microscopic haematuria always warrants further investigations.

The first step when presented with a rabbit with haematuria is to distinguish if it is true haematuria or simply red/orange pigmentation of the urine. Normal rabbit urine can have a variable appearance (Figure 2) and its colour may vary from pale yellow to orange, to dark brown and to a deep red colour that can be easily mistaken for blood. Plant pigments (for example, contained in vegetables such as beetroot, broccoli, dandelions, carrots and cabbage) can be variably excreted in the urine, giving this characteristic orange/brown/red colour (Harcourt-Brown, 2002).

Urinalysis, simply performed via a reagent strip, may reveal the presence of blood and/ or other abnormalities, thus enabling the differentiation between true haematuria and porphyrin-pigmented urine. However, false positive results can occur with haemoglobin and myoglobin, so the dipstick analysis is sensitive, but non-specific.

Some porphyrin pigments will fluoresce when exposed to a Wood's lamp's ultraviolet light and pigmented urine tends to be intermittent, only lasting three or four days (Harcourt-Brown, 2002).

Urine voided on to a clean surface may be used for analysis, but ideally, should be collected by catheterisation or cystocentesis.

However, to ensure the changes noted on the urinalysis did not simply reflect the method of collection, sediment examination for the presence of red blood cells (more than five red blood cells per high power field is reflective of true haematuria) should be performed as well.

## Origination and diagnosis

A complete history should be taken. A thorough physical examination and a full diagnostic evaluation, including haematology, serum biochemistry, bacteriologic culture of urine (sterile collection technique is mandatory), sensitivity test, plain (Figure 3) and post-contrast whole body radiographs, and ultrasonography of the reproductive and urinary tract are always recommended for a definitive diagnosis and before initiating any treatment, as findings may alter the therapeutic course and prognosis for the patient.

The primary concern is to understand whether the haemorrhage is originating from the urinary or reproductive tract, representing either haematuria or colporrhagia, respectively. Table 1 gives a list of differential diagnoses that would need to be considered when a rabbit is presented with haematuria or bloody discharge. Other vague clinical symptoms may be present concurrently with haematuria, depending on the underlying disorders, and may include lethargy, decreased appetite to anorexia, weight loss, anuria, stranguria, pollakiuria, incontinence, polyuria/polydipsia, hunched posture and bruxism, which are signs of abdominal pain.

## Reproductive factors

The reproductive anatomy of the female rabbit has unique features among placental mammals, as the uterus is bicornuate, with two distinct cervices that open separately into a long and flaccid vagina (Popesko et al, 1992). The urethra opens into the vestibulum of the vagina, therefore urine can be retained in the vagina and mix with blood coming from the uterus, complicating the determination of the source of haemorrhage in cases of bloody discharge.

Cystic endometrial hyperplasia (CEH) involves progressive thickening of the endometrium characterised by an increase in size, number and cystic dilation of the endometrial glands (Figure 4). These changes are hormonally induced and are thought to represent an exaggeration of the normal proliferative response, which occurs in the endometrium in response to chronic or repeated hormonal stimulation after repeated oestrogen cycles without pregnancy (Kustritz, 2005).

For this reason, in many species, CEH is more frequently seen in middle-aged to older animals that are nulliparous (Saito et al, 2002; Schlafer and Gifford, 2008).

Endometrial changes are supposed to occur as a continuum from polyp formation, to cystic and adenomatous hyperplasia, to adenocarcinoma in the rabbit (Kaphlake and Paul-Murphy, 2012), although this is not common opinion as other authors found no association between cystic hyperplasia and development of neoplasia, sustaining the idea adenocarcinoma is the result of senile atrophy of the endometrium (Baba and von Haam, 1972).

In other species, it is assumed the CEH-pyometra complex begins with development of endometrial hyperplasia, which causes secretions to accumulate in the uterine lumen followed by establishment of a bacterial infection. Alternatively, it has been proposed a sub-clinical, low-grade, bacterial infection may be the initial event that causes proliferation of the endometrium, changes of the uterine environment, accumulation of secretion and, ultimately, development of a massive bacterial infection and pyometra (Schlafer and Gifford, 2008).

Haematuria or serosanguineous vaginal discharge are also common clinical signs associated with uterine adenocarcinoma (Figure 5), which is considered the most common neoplasia in entire female rabbits, with an incidence as high as 50 per cent to 80 per cent in certain breeds (Kaphlake and Paul-Murphy, 2012).

Frank (or gross) blood in the urine is usually seen at the end of urination.

Other causes of uterine enlargement (for example, pregnancy/abortion (Figure 6), pyometra, metritis, hydrometra or mucometra, endometrial aneurysm, endometrial hyperplasia and other tumours) can be ruled out with an abdominal ultrasound.

Ovariohysterectomy is the treatment of choice in all these cases, as soon as the patient has been

stabilised. The tissues removed should always be submitted for histopathological examination.

## Metabolism

Rabbits have a unique calcium metabolism and have evolved a strategy in which the majority of dietary calcium is absorbed in the intestine passively and independently from vitamin D, rather than in accordance to metabolic needs, and the excess is excreted via the urine (Eckermann-Ross, 2008). Rabbits excrete about 45 per cent to 60 per cent of ingested calcium in their urine (Cheeke and Amberg, 1973), therefore normal rabbit urine is often creamy white and contains sediment as a result of precipitation of calcium carbonate (Figure 3).

Ammonium magnesium phosphate crystals are also considered a normal finding in rabbit urine (Cheeke, 1987). Sludgy urine and urolithiasis are common findings in rabbits and may result from exacerbation of physiologic calcium excretion (Hoefer, 2006). The presence of sediment and crystals, coupled with the alkaline pH of rabbit urine, increases the likelihood of stone formation in the urinary tract in rabbits (Eckermann-Ross, 2008).

Furthermore, genetic predisposition, dehydration, metabolic disorders, bacterial or parasitic infections, nutritional imbalances and any condition causing urinary stasis (for example, *Encephalitozoon cuniculi* infection, spinal abnormalities or trauma, lack of exercise or obesity) may all predispose rabbits to development of urolithiasis (Harcourt-Brown, 2005).

Urinalysis is useful to assess renal function and haematuria, and proteinuria may be associated with urolithiasis.

In many mammals, urea is commonly used to assess renal function, but rabbits have a reduced capacity to concentrate urea. Furthermore, urea follows a circadian rhythm and it largely depends on the protein intake and nutritional status of the animal ( Jenkins, 2008).

Creatinine is freely filtered through the glomerulus and excreted at a constant rate (Melillo, 2007). It is considered a more reliable indicator of kidney function, if compared to blood urea levels, because it does not show the same variability due to external extra-renal factors. At least 65 per cent to 75 per cent of the nephrons need to be damaged before a significant increase in serum creatinine is observed and changes in routine urine analysis can be detected.

In cases of renal disease, proteinuria seems to occur earlier than biochemical changes, although protein levels need to be evaluated along with urine specific gravity and sediment because healthy adult rabbits may have trace proteinuria (Kraus et al, 1984). Measuring urinary protein/ creatinine ratio (0.11 to 0.47 is reported to be normal in rabbits) may be a more useful test in clinical practice – especially in association with urine specific gravity to quantify the proteinuria.

Persistent proteinuria, in urine with inactive sediment, is indication of renal tubular or glomerular

disease and can be used as a marker of the severity of renal disease to monitor disease progression, and as an important prognostic factor (Reusch et al, 2009).

Many toxicologic studies have suggested the anatomic integrity of the kidney might be reflected by the output of urinary enzymes.

Gamma-glutamyl transferase (GGT) is one of the numerous renal tubular enzymes that are excreted in the urine of many mammal species (Bush, 1991).

The diagnostic value and clinical significance, as a valid indication of renal disease, of many different urinary enzymes has long been investigated in many mammalian species.

GGT exhibits its highest activity in the straight proximal renal tubule (Melillo, 2007), therefore a validation of a non-invasive screening test for detection of this urinary enzyme, as a possible indication of early renal damage in rabbits, could be extremely useful.

The author has completed a preliminary study to establish the reference range for GGT and GGT index (GGT to creatinine ratio) in fresh urine of healthy domestic rabbits (Mancinelli et al, 2012); however, further investigations are warranted to establish the clinical utility of these parameters.

## Treatment

Treatment is aimed at correcting perfusion, dehydration, azotaemia, electrolytes and acid-base imbalances with aggressive fluid therapy. Urine production should be monitored closely and placing premeasured absorbent pads may help to estimate the volume of urine produced. Normal rabbits produce approximately 130ml/kg/day of urine (Kaphlake and Paul-Murphy, 2012).

Antibiotics may be required in case of an infectious process and use of analgesia is to be considered, taking care of the possibly reduced renal function. In cases of urolithiasis, catheterisation of the urethra (Figure 7) may be sufficient to dislodge distally-located stones.

Surgery may be required for uroliths located elsewhere along the urinary tract and those causing obstruction. Dietary modification aimed at providing a moderate amount of calcium should be instituted.

Disseminated intravascular coagulation (Garibaldi et al, 1987) and lead poisoning, along with renal damage (Hood et al, 1997), have been reported to cause haematuria in rabbits. Urobilinuria may appear similarly as haematuria, but test results are negative for blood and positive for urobilinogen (Garibaldi et al, 1987).

Determining the source of urogenital blood can be challenging in rabbits and a full diagnostic work-up, along with history and physical examination, is essential to reach a diagnosis. Rigid endoscopy

may be helpful to the clinician as it may allow for non-invasive examination of the vagina, urethra, bladder and cervices and collection of samples for cytology, culture and histopathology (Lennox, 2005).

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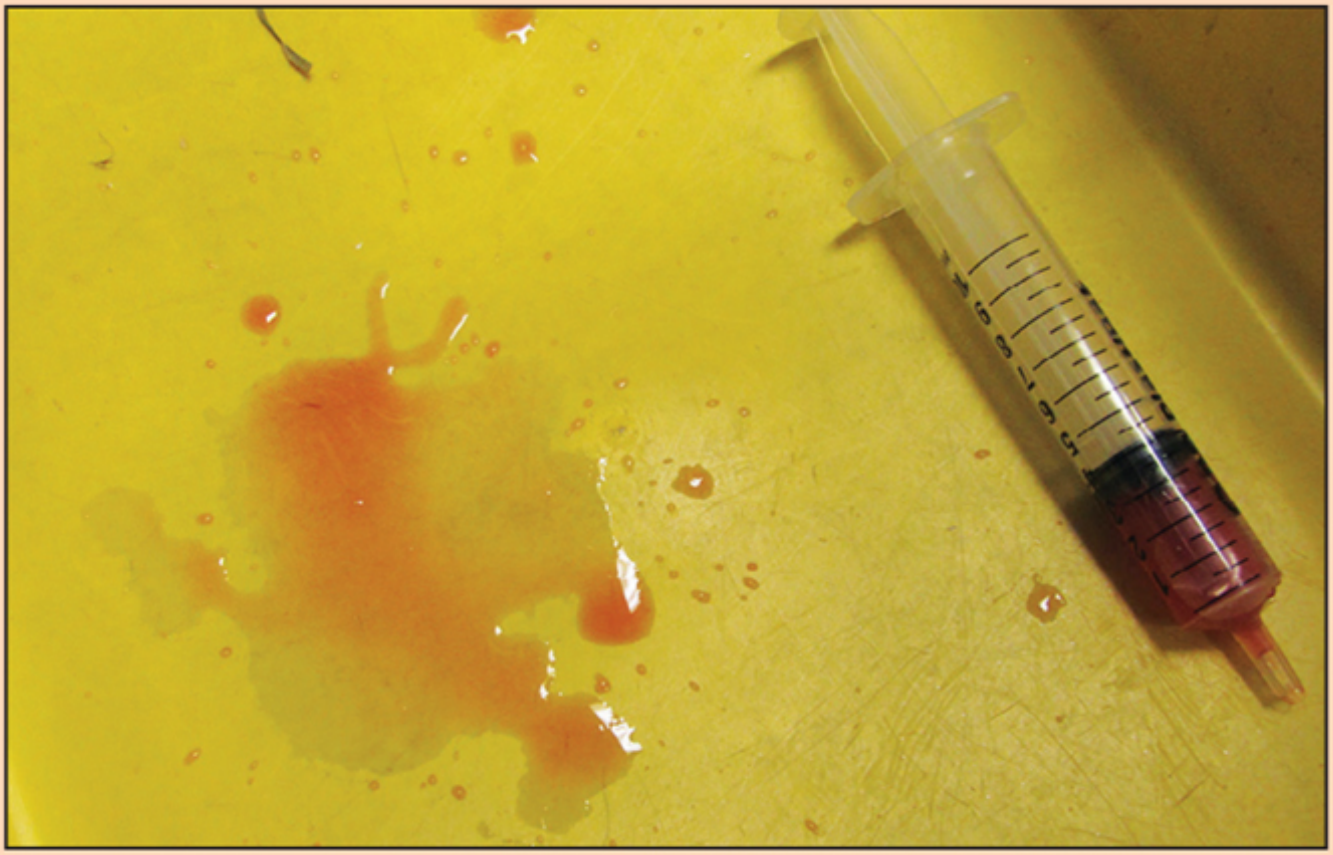

**Figure 1.** Macroscopic haematuria is grossly visible in the urine; however, the first step is to distinguish if it is true haematuria or simply red/orange pigmentation of the urine.

**Figure 2.** Normal rabbit urine can have a variable appearance and its colour may vary from pale yellow to orange, to dark brown and to a deep red colour.

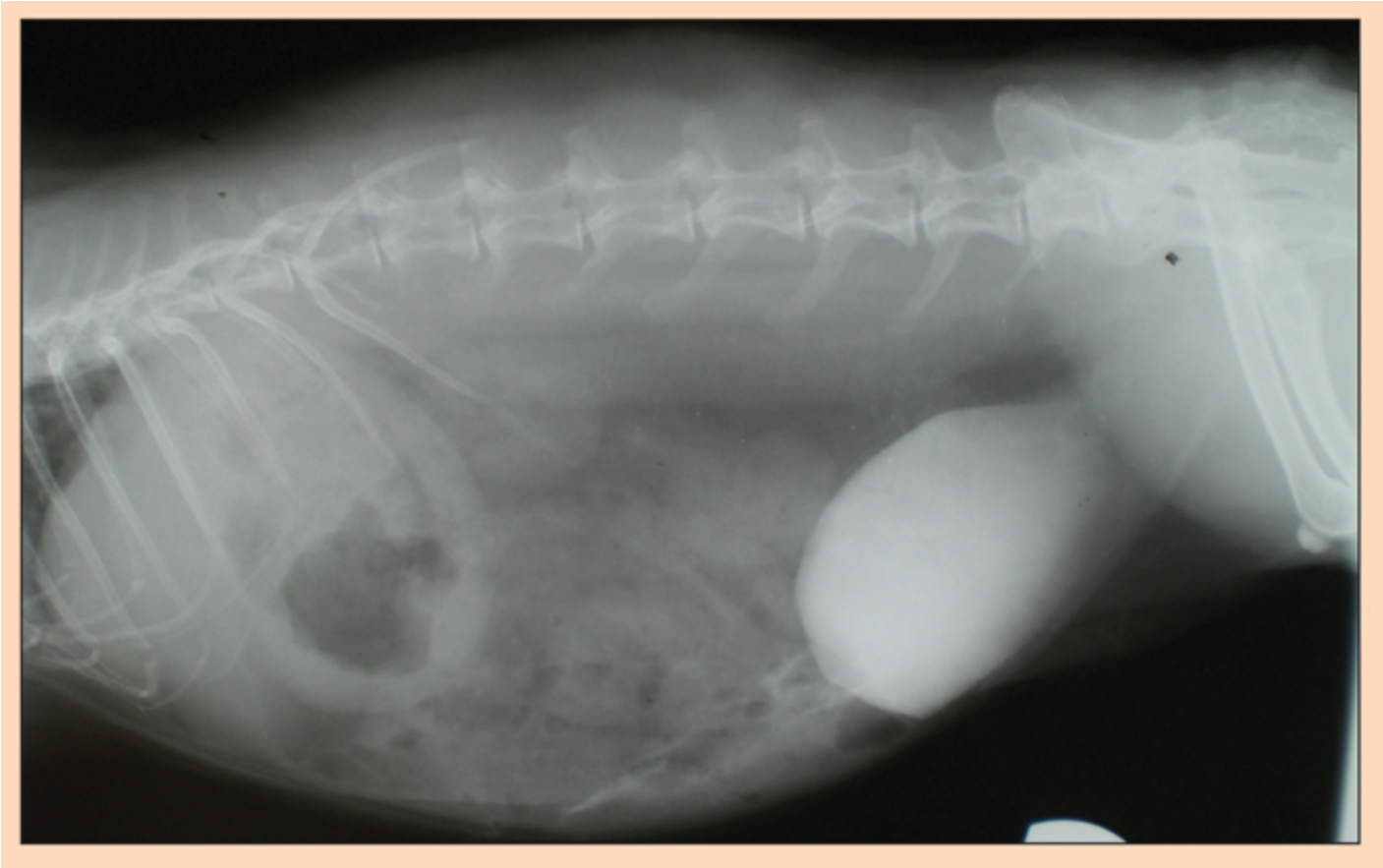

**Figure 3.** Plain right latero-lateral radiograph of a rabbit's abdomen showing radiodense urine sediment within the bladder.

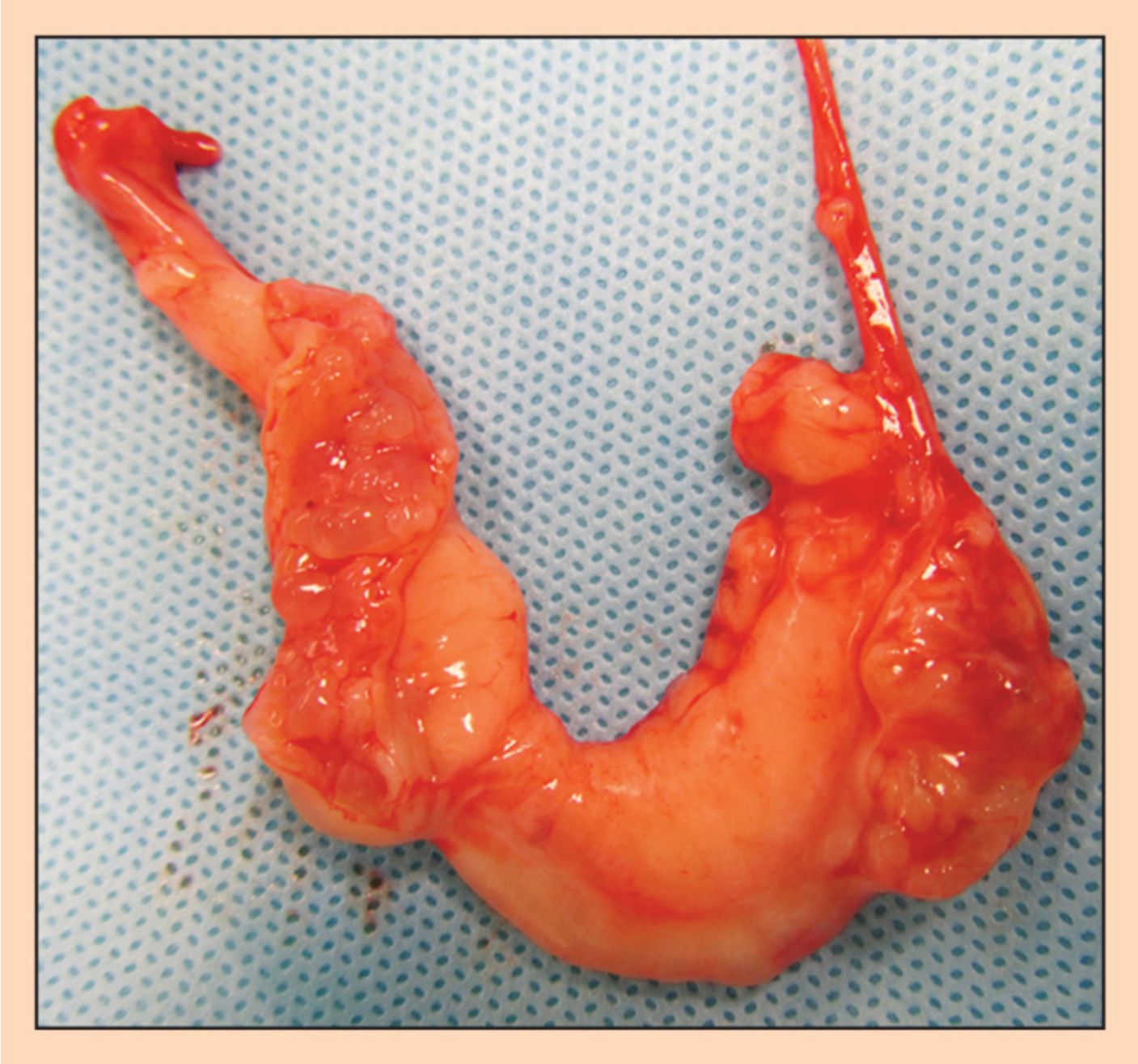

**Figure 4.** Cystic endometrial hyperplasia involves progressive thickening of the endometrium characterised by an increase in size, number and cystic dilation of the endometrial glands.

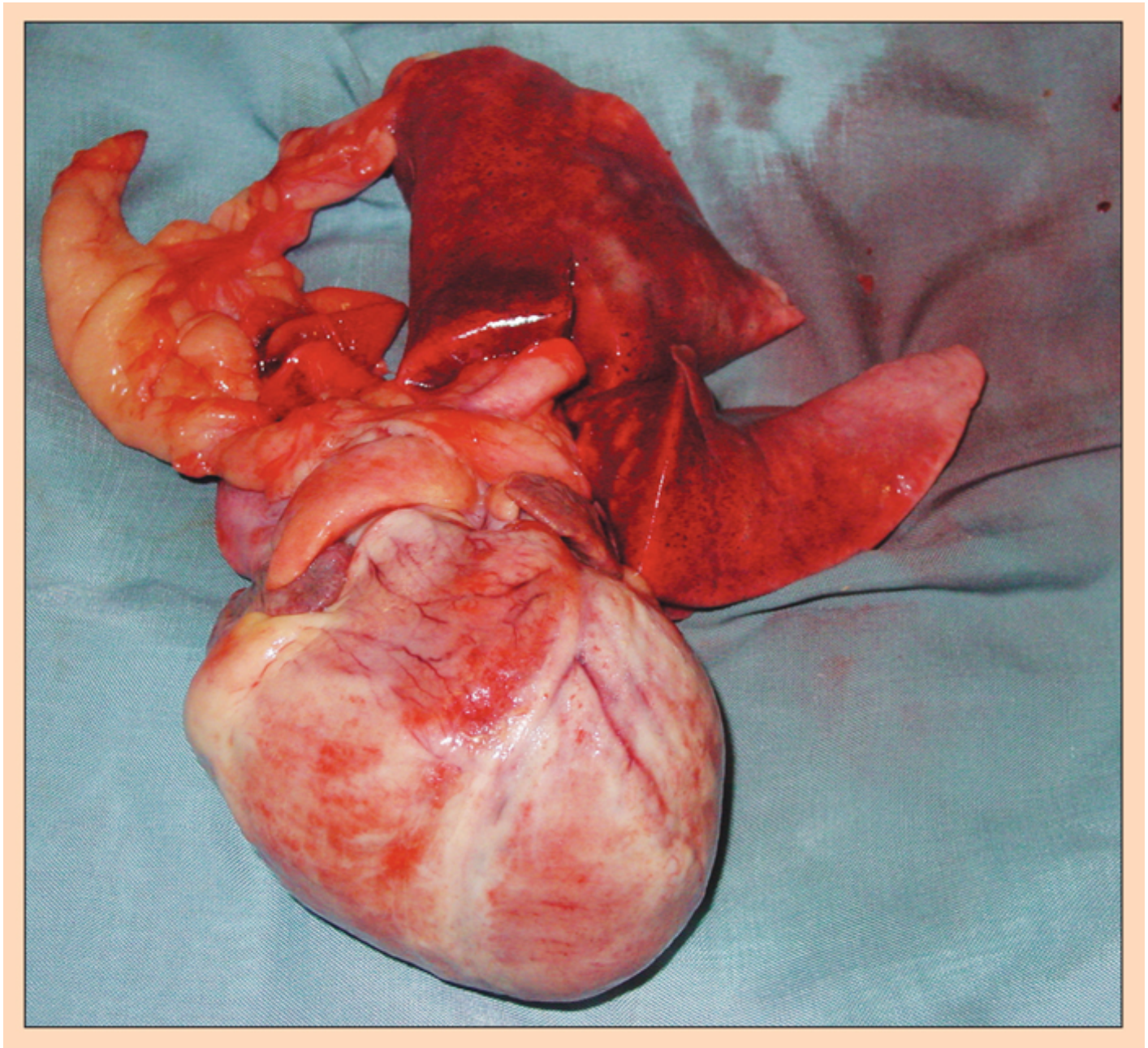

**Figure 5.** Uterine adenocarcinoma is considered the most common neoplasia in entire female rabbits, with an incidence as high as 50 per cent to 80 per cent in certain breeds.

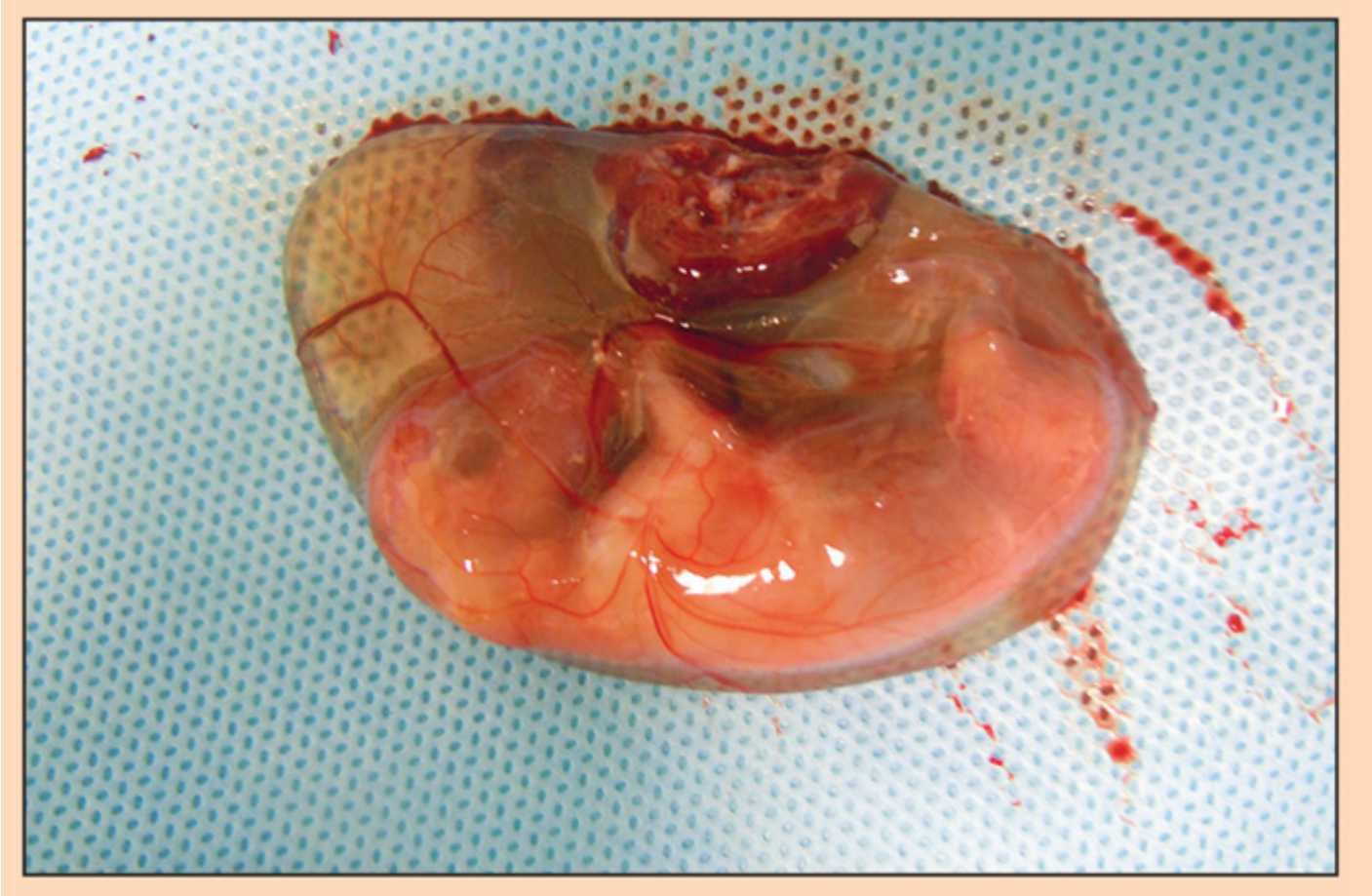

**Figure 6.** Abortion can be a cause of haematuria in rabbits.

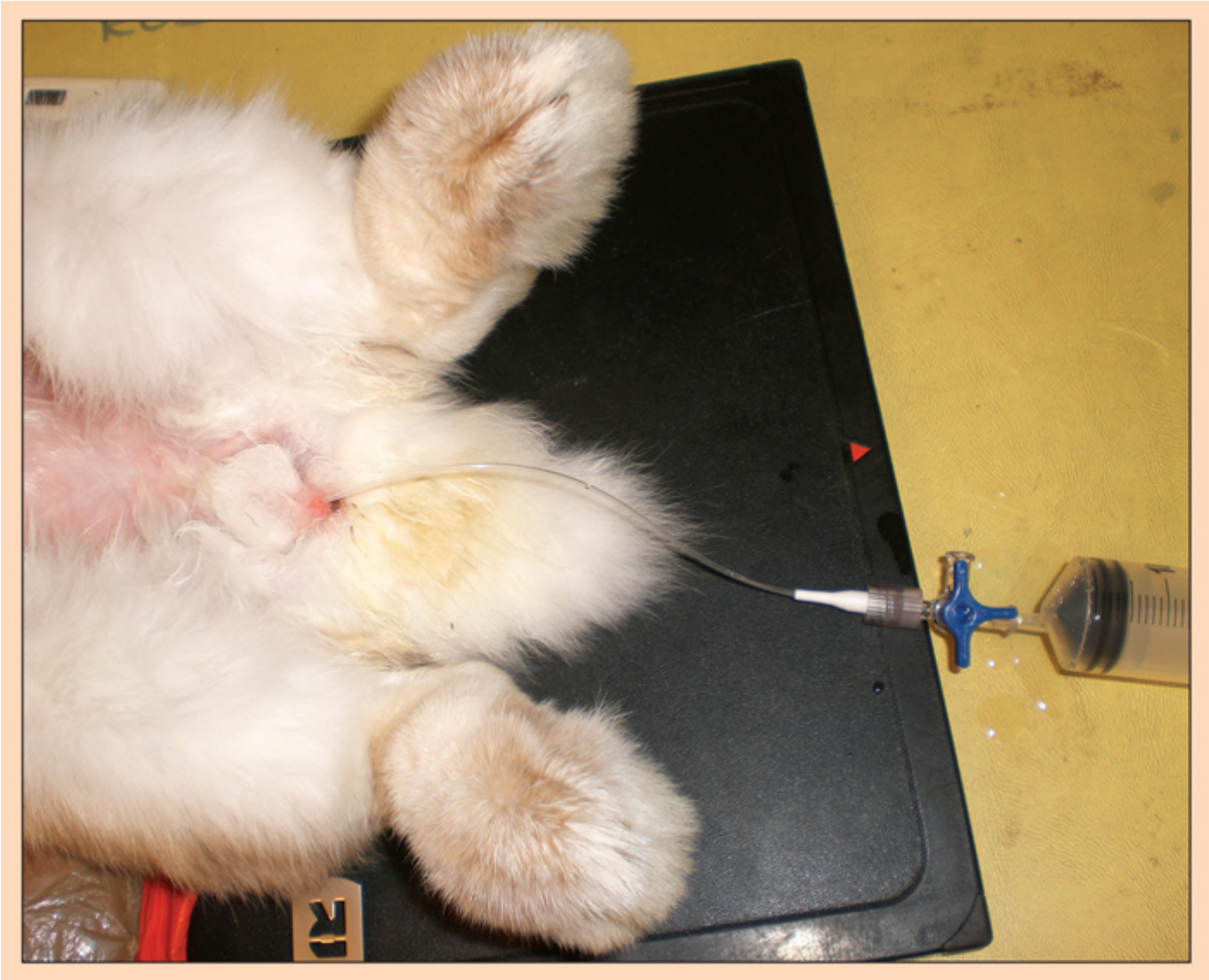

**Figure 7.** Catheterisation may be used to collect urine or dislodge stones distally located within the

urinary tract.

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|---|---|
| Urinary tract | Sludgy urine |
| | Cystitis, urethritis |
| | Chronic polypoid cystitis |
| | Glomerulopathy |
| | Nephritis/pyelonephritis (*Pasteurella*, *Staphylococcus*, *Encephalitozoon cuniculi*) |
| | Urolithiasis (bladder, urethra, ureter, renal pelvis) |
| | Renal neoplasia |
| | Renal infarcts |
| | Bladder polyps |
| | Trauma |
| Reproductive tract | Endometrial hyperplasia |
| | Purulent endometritis |
| | Uterine adenocarcinoma |
| | Endometrial venous aneurysm |
| | Endometrial haemangiomatosis |
| | Vaginal prolapse |
| | Dystocia/abortion |
| | Trauma |
| Systemic disease | Viral haemorrhagic disease |
| | Disseminated intravascular coagulation |
| | Lead poisoning |
| | Anticoagulant toxicity |
| | Sepsis |

**Table 1. A list of differential diagnoses for haematuria in rabbits (modified from Harcourt-Brown, 2002; Kaphlake and Paul-Murphy, 2012)**