Uterine disorders in 59 rabbits

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Uterine disorders in 59 rabbits

B. Walter, T. Poth, E. Böhmer, J. Braun, U. Matis

The medical records of 59 rabbits with uterine disorders were assessed retrospectively. Ten animals were presented because of vaginal discharge; the reasons for presentation of the remaining 49 rabbits included mammary masses, skin tumours, anorexia and poor general health. All the rabbits underwent a clinical examination, and 54 were examined by ultrasonography and/or radiography. Forty-five rabbits underwent ovariohysterectomy and the other 14 rabbits were euthanased, three because of pulmonary metastases and 11 because of very poor health unrelated to their uterine disease. The genital tracts of all the rabbits were submitted for histological examination. Endometrial hyperplasia (in 24 rabbits) and adenocarcinoma (in 18 rabbits) were the most common uterine disorders; in a further 11 cases both conditions were observed. The remaining six rabbits had other uterine disorders. Four rabbits that were presented with adenocarcinoma of the mammary gland were found to have concurrent uterine disorders. The mean age of the rabbits with endometrial hyperplasia was 4·5 years, and that of the rabbits with adenocarcinoma was 6·1 years. Four rabbits had ovarian tumours.

RABBITS have become popular pets and are therefore commonly seen in veterinary practice. The incidence of genital tract disorders in female rabbits is high, with uterine adenocarcinoma and endometrial hyperplasia being the most common diseases (Greene and Strauss 1949, Baba and von Haam 1972, Saito and others 2002). Haematuria and/or a serosanguineous vaginal discharge may indicate disorders of the genital tract (Saito and others 2002, Lode and others 2003, Paré and Paul-Murphy 2004).

The most common tumour of the genital tract in female rabbits is uterine adenocarcinoma (Ingalls and others 1964, Stein and Walshaw 1996). Peritoneal metastases may develop if the tumour penetrates the uterine wall, and distant metastases may be found in the lungs, liver, brain or bone marrow (Weisbroth 1994, Harcourt-Brown 2002). The development of carcinomatosis appears to be a relatively slow process (Ingalls and others 1964, Sommerville 1998).

The age of the rabbit is considered to be the most important determinant for the development of metropathy (Ingall and others 1964). Age-related changes in the endometrium may promote the formation of tumours (Baba and von Haam 1972), but no correlation between the prevalence of uterine cancer in rabbits and their breeding history has been established (Ingalls and others 1964). Saito and others (2002) diagnosed endometrial hyperplasia or uterine adenocarcinoma in 26-month-old rabbits, and Stein and Walshaw (1996) reported that up to 80 per cent of five-year-old rabbits may be affected. Baba and von Haam (1972) found no relationship between endometrial hyperplasia and the development of adenocarcinoma, although Ewringmann (2005) considered endometrial hyperplasia to be a precursor of adenocarcinoma. Pyometra, endometrial venous aneurysm and tumours such as leiomyosarcoma are the least common metropathies in rabbits (Saito and others 2002, Paré and Paul-Murphy 2004).

This paper describes a retrospective study of the clinical and histopathological findings in 59 rabbits with uterine disorders.

Materials and methods

From 2000 to 2006, 59 female rabbits (53 aged from one to 12 years, six age unknown) were presented to the Clinic for Surgery and Reproduction in Small Animals at the University of Munich; 10 were presented because of a serosanguineous vaginal discharge, four had mammary gland tumours, two were presented for elective ovariohysterectomy, 20 had disorders related to the genital tract and 23 showed signs of poor health.

After an initial clinical examination, two rabbits underwent elective ovariohysterectomy without further diagnostic work-up, and three rabbits were immediately euthanased because they were in very poor health. The other 54 rabbits were examined by radiography and/or ultrasonography. A 13·5 MHz sector transducer (Sonoline Elegra; Siemens) was used for transabdominal ultrasonography. Radiographs were taken with a Polymat 70 (Siemens). Fifteen rabbits were examined only by transabdominal ultrasonography, only radiographs were taken in 19 rabbits, and both diagnostic methods were used in 20 rabbits. When a tumour was suspected (Fig 1), a minimum of two radiographic views of the thorax were also taken to detect possible metastases.

After radiographic and/or ultrasonographic examination, 11 rabbits were euthanased, three because of evidence of pulmonary metastases and eight because of very poor health (Table 1). The remaining 43 rabbits underwent ovariohysterectomy via a ventral midline incision under general anaesthesia; the two rabbits presented for elective ovariohysterectomy underwent the same surgery (Table 1). The abdominal wall including the peritoneum was closed in a simple continuous suture pattern and the skin was closed in a simple interrupted suture pattern. Postoperative care included analgesia, administration of an electrolyte solution and antibiotic treatment.

In each case the genital tract was submitted for gross and histopathological examination. The rabbits that were euthanased were subjected to a complete postmortem examination, including his-

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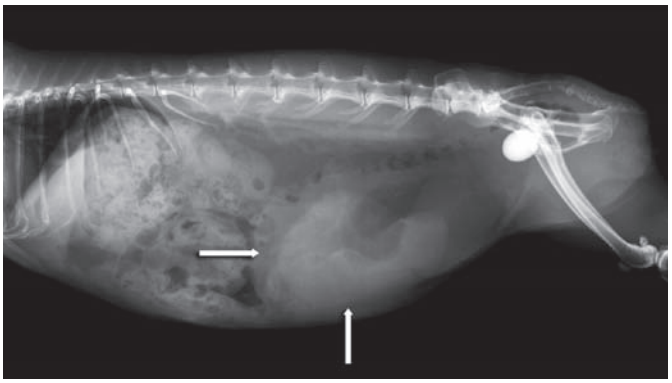

FIG 1: Laterolateral radiograph of the abdomen of a six-year-old female rabbit with adenocarcinoma of the uterus (arrows) and a urolith in the urinary bladder.

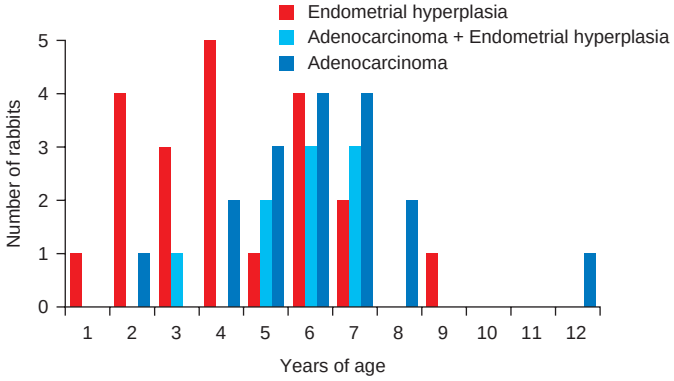

FIG 2: Age distribution of rabbits with adenocarcinoma (n=17), endometrial hyperplasia (n=21) or concurrent adenocarcinoma and endometrial hyperplasia (n=9).

TABLE 1: Treatment of 59 rabbits with uterine disorders, and the reasons for the treatment chosen

Intervention	Underlying reason	Number (%) of rabbits
Ovariohysterectomy	Elective ovariohysterectomy	2 (3·4)*
Ovariohysterectomy	Uterine disorder diagnosed	43 (72·8)
Euthanasia	Poor prognosis because of severe systemic disease (encephalitozoonosis, malocclusion)	3 (5·1)*
Euthanasia	Poor prognosis because of severe systemic disease (cardiopathy, encephalitozoonosis, peritoneal metastases, malocclusion, rabbit haemorrhagic disease, tumours of the liver and the urinary bladder)	8 (13·6)†
Euthanasia	Metastases in the lungs	3 (5·1)†

* These rabbits underwent only clinical examination before euthanasia
† Euthanased after ultrasonography and/or radiography

TABLE 2: Results of histopathological examination in 59 female rabbits with uterine disorders

Type of metropathy	Additional tumours of the uterus, ovaries and/or mammary gland	Number (%) of rabbits
Endometrial hyperplasia	None	23 (42·5)
Endometrial hyperplasia	Uterus: haemangioma	1 (1·7)
Adenocarcinoma	None	11 (18·7)
Adenocarcinoma	Mammary gland: adenocarcinoma	2 (3·4)
Adenocarcinoma	Ovaries: granulosa cell tumour	3 (5·1)
Adenocarcinoma	Ovaries: adenocarcinoma	1 (1·7)
Adenocarcinoma	Uterus: squamous cell carcinoma	1 (1·7)
Adenocarcinoma + endometrial hyperplasia	None	9 (15·3)
Adenocarcinoma + endometrial hyperplasia	Mammary gland: adenocarcinoma	2 (3·4)
Pyometra	None	4 (6·8)
Carcinosarcoma	None	1 (1·7)
Adenoma	None	1 (1·7)

topathological examination of the genital tract. Representative samples of the genital tract were fixed in 7 per cent buffered formaldehyde solution, embedded in paraffin, cut into sections 4 to 6 µm thick and routinely stained with haematoxylin and eosin.

Data on the survival time of the rabbits with adenocarcinoma of the uterus were collected from their owners.

Results

The age distribution of the rabbits with different uterine disorders is shown in Fig 2. The youngest rabbit was one year of age and had endometrial hyperplasia. All of the rabbits with uterine adenocarcinoma were at least two years of age.

Thirty-five rabbits were examined by abdominal ultrasonography; uterine abnormalities, which included enlargement of the uterus, with hyperechoic and hypoechoic areas, were found in all cases. Solid masses with a minimum diameter of 2 cm were detected by ultrasonography in the uterus of 13 of the rabbits. Ten rabbits had ultrasonographic findings consistent with intrauterine fluid; nine of these had had a vaginal discharge on presentation. The ovaries of one rabbit had numerous cysts, and a granulosa cell tumour was diagnosed on histological examination of this case.

Abdominal radiographs were taken in 39 rabbits and revealed an enlarged uterus in 32 cases. Of these, 14 had endometrial hyperplasia alone, 15 had adenocarcinoma, one had pyometra, one had adenoma, and one had carcinosarcoma of the uterus.

The uteri of all 59 rabbits were examined either after ovariohysterectomy or as part of a postmortem examination after euthanasia (Table 2). In 24 cases, there was moderate to severe polypoid and cystic endometrial hyperplasia, with protrusions of the endometrium into the lumen and dilation of numerous endometrial glands with mucus (Fig 3); the mean age of the affected animals was 4·5 years (Fig 2). One of these rabbits had a cavernous uterine haemangioma with thrombus formation. Twenty-nine rabbits had adenocarcinoma of the uterus, often with widespread foci of necrosis and multifocal infiltration of the myometrium (Fig 4); the mean age of these rabbits was 6·1 years. Fifteen rabbits had solitary tumours, with a diameter of 2 to 5 cm, in one or both uterine horns. Uterine adenocarcinoma was sometimes accompanied by squamous cell carcinoma (one case) or endometrial hyperplasia (11 cases) (Fig 5). In addition, four cases of pyometra, one of carcinosarcoma and one of adenoma were confirmed (Table 2).

All 118 of the rabbits' ovaries were examined. Three cases with an ovarian granulosa cell tumour and one with ovarian adenocarcinoma were identified; in each case the rabbit also had uterine adenocarcinoma.

Four rabbits had mammary gland neoplasia, which was diagnosed as adenocarcinoma in each case. Two of these rabbits also had uterine adenocarcinoma, and two had a combination of uterine adenocarcinoma and endometrial hyperplasia.

Fourteen rabbits were examined postmortem. In three cases, the radiographic diagnosis of pulmonary metastases was confirmed postmortem. In two cases, peritoneal metastases were detected during postmortem examination; one of these rabbits also had metastases in the lungs. The causes of poor health that led to euthanasia in the other rabbits included cardiopathy, encephalitozoonosis, malocclusion, rabbit haemorrhagic disease, and tumours of the liver and the urinary bladder (Table 1).

Eight of the 29 rabbits with adenocarcinoma were euthanased immediately after the initial examinations, either because metastases had been detected or because they were in very poor health. Survival data were available for the remaining 21 rabbits with uterine adenocarcinoma that underwent ovariohysterectomy. Three rabbits died during the first week after surgery, one because of a skin laceration and two of unknown causes. Four rabbits were euthanased, two, three, five, and eight months after the initial examination, because metastases in the lungs were diagnosed by radiography. Four rabbits were euthanased for other reasons, and five rabbits died of unknown causes several months postoperatively. Five rabbits were still alive when the owners were contacted.

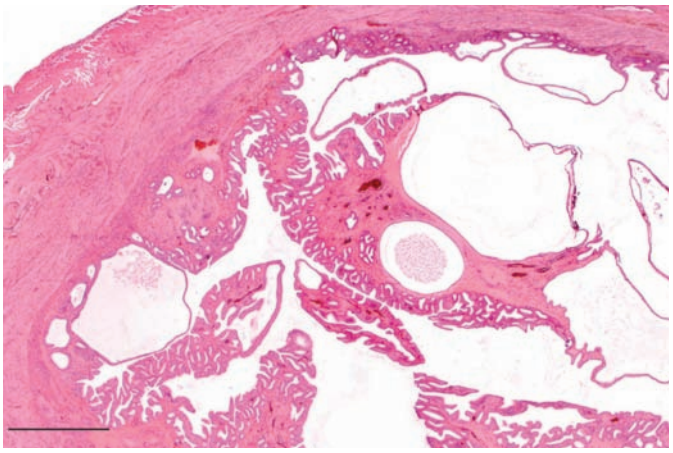

FIG 3: Endometrial hyperplasia in a six-year-old rabbit. Haematoxylin and eosin. Bar=1 mm.

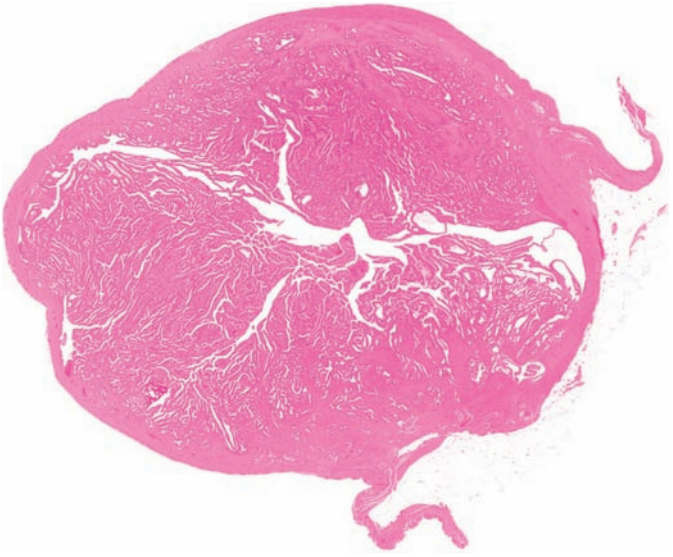

FIG 4: Uterine adenocarcinoma in a five-year-old rabbit. Haematoxylin and eosin. Subgross photograph

Overall, eight of 29 rabbits with uterine adenocarcinoma survived for 22 months or longer after surgery.

Discussion

Female rabbits are non-seasonally polyoestrous and are induced ovulators. Mounting by other rabbits of either sex, or handling, can induce ovulation, which is followed by pseudopregnancy lasting 15 to 17 days if fertilisation has not occurred. Pseudopregnancy may induce galactopoiesis (Patton 1994, Ewringmann 2005), which is accompanied by proliferation of the endometrial glands and glandular secretion. It is not known whether repeated pseudopregnancy and the associated changes contribute to pathological alterations of the endometrium and mammary glands in older rabbits.

The results of the present study were in agreement with previously reported findings that endometrial hyperplasia is a common disease of rabbits older than three or four years and is sometimes seen in rabbits less than one year of age (Saito and others 2002, Lode and others 2003). Greene (1958) showed that the incidence of uterine adenocarcinoma increased considerably with age; in the present study, the incidence of uterine adenocarcinoma in rabbits two to three years of age was 4·2 per cent and increased to 79·1 per cent in rabbits five to six years of age. It is not clear whether endometrial hyperplasia progresses to adenocarcinoma in rabbits. The results of the present study do not provide unequivocal evidence for sequential development of these two uterine disorders; adenocarcinoma can clearly develop independent of endometrial hyperplasia (18 cases in the present study) and both conditions can occur simultaneously (11 cases). However, malignant

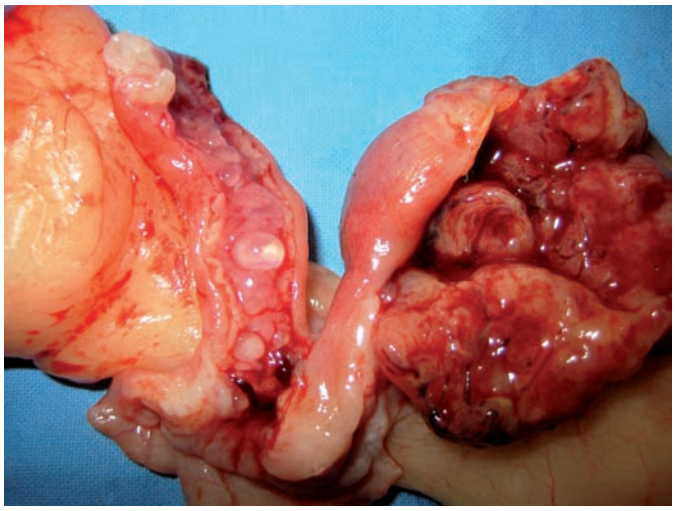

FIG 5: Gross postmortem appearance of the uterus of a six-year-old rabbit, showing multiple endometrial cysts in the left horn and an adenocarcinoma in the right horn.

transformation of hyperplastic epithelial cells in the endometrium cannot be excluded, and requires further investigation. The presence of oestrogen receptor α and progesterone receptors in normal uterine tissue, hyperplastic endometrium and uterine adenocarcinoma was investigated in rabbits by Asakawa and others (2008). Both types of receptors were detected in 59·3 per cent of normal uteri and 68·4 per cent of uteri with endometrial hyperplasia, whereas 80·8 per cent of tissue samples with papillary adenocarcinoma were negative for both receptors, and 93·8 per cent of the tubular/solid adenocarcinomas examined were positive for one or both of the receptors. Those results suggest that hormonal stimulation could be involved in the pathogenesis of tubular or solid adenocarcinomas, similar to the pathogenesis of endometrial hyperplasia.

Rabbits may be presented to a veterinarian because of a serosanguineous vaginal discharge or haematuria (Garibaldi and others 1987), signs that are often associated with endometrial hyperplasia or uterine adenocarcinoma (Saito and others 2002, Lode and others 2003). However, in the present study only 10 of the 59 rabbits showed these signs, and they therefore cannot be considered hallmark signs of uterine disease in rabbits. Diagnostic aids such as ultrasonography and/or radiography should be used if intact doe rabbits are presented with non-specific clinical signs.

Transabdominal ultrasonography appears to be an excellent method for diagnosing uterine disorders; this imaging technique was used to examine 35 of the rabbits in the present study and detected uterine abnormalities in all of them. Saito and others (2002) were able to diagnose uterine abnormalities by ultrasonography in 21 of 24 rabbits examined. Abdominal radiography was less sensitive than ultrasonography in the present study, and revealed an enlarged uterus in only 32 of 39 cases. However, Streicher and Hach (2006) concluded that abdominal palpation and radiography are particularly suitable methods for diagnosing uterine adenocarcinoma.

Mammary gland abnormalities are often associated with endometrial hyperplasia or adenocarcinoma in rabbits (Greene and Strauss 1949, Stein and Walshaw 1996, Saito and others 2002). Saito and others (2002) reported that 15 of 47 rabbits with adenocarcinoma also had mammary disorders. In the present study, adenocarcinoma of the mammary gland (four cases) was always associated with uterine adenocarcinoma.

Ovarian tumours have been described in rabbits, but the incidence seems to be low (Saito and others 2002, Greene and Strauss 1949). Granulosa cell tumours have been induced experimentally in rabbits (Peckham and others 1948, Peckham and Greene 1952). In the present study, three rabbits had a granulosa cell tumour and another had ovarian adenocarcinoma. Granulosa cell tumours have been reported in horses, dogs and cats (Patnaik and Greenlee 1987). These tumours are hormonally active and usually do not metastasise (Noakes and others 2001). In the present study, four of 59 rabbits (6·8 per cent)

had ovarian tumours. Further studies are required to determine the prevalence of ovarian tumours in rabbits and whether these tumours are hormonally active.

Eight of the 29 rabbits with uterine adenocarcinoma survived for 22 to 27 months after ovariohysterectomy. These results suggest that euthanasia should not be recommended in rabbits with uterine adenocarcinoma unless metastases are detected. The prognosis after ovariohysterectomy in older rabbits with uterine adenocarcinoma is fair to good provided that there are no metastases (Sommerville 1998). Saito and others (2002) reported a mortality of 21·3 per cent in rabbits that underwent ovariohysterectomy in an attempt to treat uterine adenocarcinoma. Follow-up examination of rabbits at regular intervals, for example, every six months, is recommended because early metastases may not be seen on thoracic radiographs at the time of surgery (Paré and Paul-Murphy 2004). In the present study, four rabbits were diagnosed with pulmonary metastases, two, three, five and eight months after ovariohysterectomy.

The results of the present study show that uterine disorders can occur in young rabbits, and disease may be subclinical in its early stages. Female rabbits unintended for breeding should therefore be neutered before one year of age. Regular ultrasonographic examination of the genital tract is recommended for rabbits whose owners do not elect ovariohysterectomy.

References

ASAKAWA, M. G., GOLDSCHMIDT, M. H., UNE, Y. & NOMURA, Y. (2008) The immunohistochemical evaluation of estrogen receptor-α and progesterone receptors of normal, hyperplastic, and neoplastic endometrium in 88 pet rabbits. *Veterinary Pathology* **45,** 217-225

BABA, N. & VON HAAM, E. (1972) Animal model for human disease: spontaneous adenocarcinoma in aged rabbits. *American Journal of Pathology* **68,** 653-656

EWRINGMANN, A. (2005) Vaginalausfluss. In Leitsymptome beim Kaninchen. Ed A. Ewringmann. Enke Verlag. pp 125-136

GARIBALDI, B. A., FOX, J. G., OTTO, G., MURPHY, J. C. & PECQUET-GOAD, M. E. (1987) Hematuria in rabbits. *Laboratory Animal Science* **37,** 769-772

GREENE, H. S. N. & STRAUSS, J. S. (1949) Multiple primary tumors in the rabbit. *Cancer* **2,** 673-691

GREENE, H. S. N. (1958) Adenocarcinoma of uterine fundus in the rabbit. *Annals of the New York Academy of Sciences* **75,** 535-542

HARCOURT-BROWN, F. (2002) Reproductive disease. In Textbook of Rabbit Medicine. Ed F. Harcourt-Brown. Butterworth-Heinemann. pp 348-351

INGALLS, T. H., ADAMS, W. M., LURIE, M. B. & IPSEN, J. (1964) Natural history of adenocarcinoma of the uterus in the Phipps rabbit colony. *Journal of the National Cancer Institute* **33,** 799-806

LODE, J., SASSENBURG, L., MÜNNICH, A. & HAIDER, W. (2003) Endometriale Hyperplasie beim Kaninchen – eine Darstellung von acht Fällen. *Kleintierpraxis* **48,** 185-244

NOAKES, D., PARKINSON, T. & ENGLAND, G. (2001) Infertility in the bitch and queen. In Arthur's Veterinary Reproduction and Obstetrics. 8th edn. Eds D. Noakes, T. Parkinson, G. England. Saunders. pp 639-660

PARÉ, J. A. & PAUL-MURPHY, J. (2004) Disorders of the reproductive and urinary systems. In Ferrets, Rabbits and Rodents: Clinical Medicine and Surgery. 2nd edn. Eds K. E. Quensberry, J. W. Carpenter. Saunders. pp 183-193

PATNAIK, A. K. & GREENLEE, P. G. (1987) Canine ovarian neoplasms: a clinicopathologic study of 71 cases, including histology of 12 granulosa cell tumors. *Veterinary Pathology* **24,** 509-514

PATTON, N. M. (1994) Colony husbandry. In The Biology of the Laboratory Rabbit. Eds D. H. Ringler, P. J. Manning, C. E. Newcomer. Academic Press. pp 27-45

PECKHAM, B. M., GREENE, R. B. & JEFFRIES, M. E. (1948) Granulosa cell tumors in female rats and rabbits. *Science* **26,** 319-320

PECKHAM, B. M. & GREENE, R. R. (1952) Experimentally produced granulosa-cell tumors in rabbits. *Cancer Research* **12,** 654-656

SAITO, K., NAKANISHI, M. & HASEGAWA, A. (2002) Uterine disorders diagnosed by ventrotomy in 47 rabbits. *Journal of Veterinary Medical Science* **64,** 495-497

SOMMERVILLE, L. M. (1998) Treatment of uterine adenocarcinoma in a domestic rabbit by ovariohysterectomy. *Veterinary Record* **142,** 550-551

STEIN, S. & WALSHAW, S. (1996) Rabbits. In Handbook of Rodent and Rabbit Medicine. 1st edn. Eds K. Laber-Laird, M. M. Swindle, P. Flecknell. Pergamon Press. pp 183-217

STREICHER, M. & HACH, V. (2006) Das Uterus-Adenokarzinom des Kaninchens. *Kleintierpraxis* **51,** 305-314

WEISBROTH, S. H. (1994) Neoplastic disease. In The Biology of the Laboratory Rabbit. Eds D. H. Ringler, P. J. Manning, C. E. Newcomer. Academic Press. pp 259-292