Prospective survey of neoplastic and non-neoplastic uterine disorders in 116 domestic rabbits (Oryctolagus cuniculus)

Mäkitaipale, Johanna

2022-04

Mäkitaipale , J , Airas , N , Engblom , S & Linden , J 2022 , ' Prospective survey of neoplastic and non-neoplastic uterine disorders in 116 domestic rabbits (Oryctolagus cuniculus) ' , Journal of Exotic Pet Medicine , vol. 41 , pp. 3-8 . https://doi.org/10.1053/j.jepm.2022.01.001

http://hdl.handle.net/10138/347224
https://doi.org/10.1053/j.jepm.2022.01.001

Journal of Exotic Pet Medicine 41 (2022) 3–8

Contents lists available at ScienceDirect

Journal of Exotic Pet Medicine

journal homepage: www.elsevier.com/locate/jepm

Research

Prospective survey of neoplastic and non-neoplastic uterine disorders in 116 domestic rabbits (*Oryctolagus cuniculus*)

Johanna Mäkitaipale [a,*], Niina Airas [b], Sanna Engblom [b], Jere Lindén [b,c]

[a] Faculty of Veterinary Medicine, Department of Equine and Small Animal Medicine, University of Helsinki Finland
[b] Faculty of Veterinary Medicine, Department of Veterinary Biosciences, University of Helsinki, Finland
[c] Finnish Centre for Laboratory Animal Pathology, University of Helsinki, Finland

ARTICLE INFO

Keywords:
Adenocarcinoma
Cystic endometrial hyperplasia
Rabbit
Reproduction
Uterine disorder

ABSTRACT

Background: Earlier studies indicate that the risk for uterine tumours in rabbits may be as high as 60–80%. This high occurrence and the need for routine neutering of non-breeding pet rabbits have recently been in the spotlight.

Methods: This study aimed to describe and compare macroscopic and histopathological alterations in uteri collected from domestic rabbits of various ages that were neutered, deceased, or euthanized without a suspected uterine disorder (NoUD; n = 94) and from rabbits with a suspected uterine disorder (UD; n = 22).

Results: In the NoUD group, uteri of 41 rabbits (44%) displayed histopathological findings and 12 rabbits (13%) had neoplasms. Samples from thirteen rabbits (14%) evinced histopathological findings with no macroscopic alterations. The most frequent diagnoses were cystic endometrial hyperplasia (26% of the 41 uteri), adenocarcinoma (9%), and polyps (5%). In the UD group, uteri from 21 (95%) out of 22 rabbits exhibited pathological alterations; in 2 (10%) of these, the changes (cystic endometrial hyperplasias) were seen only in histology. The most frequent diagnoses in the uteri of the UD group were cystic endometrial hyperplasia (77%) and adenocarcinoma (54%). Uterine malignant neoplasia affected 40% of all rabbits aged over 3 years, and the odds of a malignant uterine tumour in these rabbits were approximately 19-fold higher than in rabbits aged under 3 years.

Conclusions and clinical relevance: Uterine disorders are common in domestic rabbits, even without a suspected uterine disease, and the risk of uterine neoplasia markedly increases after 3 years of age. A macroscopically normal uterus may have pathological changes and ovariohysterectomy should be therefore preferred over ovariectomy at least in older rabbits.

Introduction

Even a century ago, studies showed that in rabbits the uterus is the most common site for primary tumours [1,2]. In rabbits aged over four years, the prevalence of uterine disorders, especially tumours, may be as high as 60–80% [3,4], and a marked increase was seen also after three years in a recent large retrospective study [5]. However, this high prevalence has recently been questioned and much discussion has arisen regarding the need for neutering female pet rabbits for tumour prevention [6,7,8,9,10,11]. In contrast to pet rabbits, infectious diseases of the uterus and problems related to pregnancy, e.g., extrauterine pregnancy and uterine torsion, are the major reproductive ailments of farmed rabbits [12]. This difference appears to result from the lower life expectancy and higher reproduction rates in farmed rabbits, whereas the longer life of pet rabbits entails an increased risk for tumours. Among these, adenocarcinomas are reported most commonly along with several other neoplastic, hyperplastic, and other non-neoplastic disorders such as hydrometra, endometrial venous aneurysm, leiomyoma, and leiomyosarcoma [5,13,14,15]. In young pet rabbits, cystic endometrial hyperplasia is the most common uterine disorder and can appear in animals as young as one year [5,14].

Several retrospective studies and case reports describe uterine disorders in farmed and pet rabbits [1,3,5,13,14,15,16,17,18]. However, the rabbits are either old or from breeding farms, or the study is based on retrospective data. Bertram et al. [5] recently published a study of uterine disorders in pet rabbits. Despite the large sample size, the study was retrospective and included post-mortem examinations and genital tract biopsy samples, hence the need for a prospective prevalence study correlating the specific clinical signs suggesting possible uterine disorders with pathology results.

The aim of this prospective study was to thoroughly examine and describe uterine pathologies in rabbits of various ages. We also aimed to report and compare the prevalence of uterine pathology in rabbits that

* Corresponding author. J. Mäkitaipale, Tel.: +358-020-1800730.
E-mail address: johanna.makitaipale@helsinki.fi (J. Mäkitaipale).

https://doi.org/10.1053/j.jepm.2022.01.001
Received 13 September 2021; Accepted 19 January 2022

were neutered, euthanized, or died with or without specific clinical signs suspective for uterine disease.

Materials and methods

Samples

The study comprised of rabbit uteri collected from 116 domestic rabbits sampled with owners' permission during ovariohysterectomy, euthanasia or after death between September 2014 and November 2015. None of the animals were operated on or euthanised only for this study. Instead, samples were collected from rabbits undergoing the above procedures for other reasons. The samples came through 12 collaborating veterinarians (71 cases) or originated from six rabbit breeders (35 cases), and a further 10 were provided by rabbit owners who wanted to participate after neutering, euthanasia, or death of their pet rabbits. Only uteri were collected for this study and authors were, therefore, unaware of any other possible diseases of these rabbits diagnosed or suspected by the submitters. Collaborating veterinarians were advised to collect the whole uterus from all intact female rabbits over four months of age presented for ovariohysterectomy or euthanasia during this period without case selection. Background information on most rabbits (n = 107), including date of birth, breed and breeding history, and a possible reason for neutering or euthanasia was received from the owners via an internet-based questionnaire. Rabbits were divided into two groups depending on the reason for neutering or euthanasia. The 'no uterine disease' group (NoUD) consisted of rabbits that underwent routine neutering, were euthanised without any specific clinical signs related to the uterine disease, or died at home without any previous signs indicating a uterine disease. The 'uterine disease' group (UD) included rabbits neutered or euthanised due to a suspected uterine disease based on specific clinical signs observed by their owner or collaborating veterinarian. Decision criteria for uterine disease as well as results of possible further examinations made by collaborating veterinarians including clinical examination, blood sample analysis, or diagnostic imaging are not available. The observed specific clinical signs are specified in the Results section.

Macroscopic and histological examination

Tissue samples were fixed in 10% neutral buffered formalin immediately after collection. Specimen containers were numbered sequentially and sent to the Department of Veterinary Biosciences, in the Faculty of Veterinary Medicine, University of Helsinki. After fixation, all samples were examined macroscopically in the same manner by two of the authors; all variations in size, shape, colour, and consistency of the uterus were recorded. At least two tissue samples were taken from both uteri (both uterine horns) for histological examination and they were opened to evaluate the endometrium. All macroscopic changes were sampled separately. Samples for histology were embedded in paraffin wax, cut into 4 μm sections, and stained with haematoxylin and eosin (HE).

Histological samples were evaluated blinded based on the sequential numbering of the uteri. All sections taken from each uterus (minimally four corresponding to two for each uterus) were evaluated and an exhaustive list of morphological diagnoses was formulated for each uterus. The sections were examined by one of the authors and diagnosis was confirmed using peer-review when needed.

Statistical methods

Mean, standard deviation (SD) and range were used as descriptive statistics in the tables. We compared the ages of rabbits in different groups employing t-tests. Fisher's exact tests were used to assess breed predilection of neoplastic and non-neoplastic uterine alterations as well as coexistence of adenocarcinoma and cystic endometrial hyperplasia. Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated based on the Mantel-Haenszel Common Odds Ratio estimate. Three years was selected as the cut-off point in the tumour prevalence comparisons, as previous studies have shown that health disorders in general significantly increase in rabbits after three years of age [5,19]. The statistical analyses were conducted with SPSS software (IBM SPSS Statistics, Version 25.0, Armonk, NY, USA). P values < 0.05 were considered statistically significant.

Results

The NoUD group consisted of uteri from 94 rabbits that underwent routine neutering (n = 57), were euthanised without any health disorders or specific clinical signs related to the uterine disease (n = 35) or died at home without any previous signs of uterine disease (n = 2). The UD group included uteri from 22 rabbits neutered or euthanised due to reproductive problems (n = 5), pseudopregnancy (n = 1), uterine disease diagnosed by a collaborating veterinarian (n = 8), mammary gland tumour (n = 4) or a combination of these (n = 4). The reported reproductive problems comprised small litters (n = 1), stillborn kits (n = 1) and infertility (n = 3).

Age range of the rabbits participating in this study was 0.4–10.0 years (mean 3.1 years, SD 2.4 years, age missing in 6 cases). The rabbits represented 18 different breeds (breed missing in 7 cases), the most common of which were mixed breed (n = 36, 31.0%), Dwarf Lops (n = 20, 17.2%), and Lionheads (n = 15, 12.9%). Other breeds were Netherland Dwarf (n = 7), Angora (n = 5), Himalayan (n = 5), Argente Champagne (n = 3), Mini Rex (n = 3), Cashmere Miniature Lop (n = 2), French Lop (n = 2), New Zealand White (n = 2), Rex (n = 2), Vienna (n = 2), Californian (n = 1), Holland (n = 1), Kleinschecken (n = 1), Lion Lop (n = 1) and Satin (n = 1). Samples collected and sent to this study consisted of 111 samples with both uteri (both uterine horns), 4 samples with only one uterus and one large sample consisting of tumour tissue only.

The mean age of rabbits in NoUD group was lower (2.6 years) ($P < 0.01$) than the mean age (5.3 years) of rabbits in UD group (Tables 1 and 2). Correspondingly, the mean age of rabbits that underwent routine neutering was 2.3 years (SD 1.6, range 0.4–7.6) and did not differ markedly from other rabbits in the NoUD group ($P = 0.141$). Of altogether 111 rabbits, 27 (24.3%) had been pregnant or had litters; seven of these rabbits had uterine disorder ($P = 0.396$). Data on pregnancy and litters were missing for five rabbits.

In the NoUD group, uteri of 41 (44%) out of the 94 rabbits showed pathological findings in the histopathological examination, and the proportion was very similar in the routine neutering subgroup (42%, 24/ 57 rabbits). The most frequent pathological findings in the NoUD group were cystic endometrial hyperplasia (n = 24, 26%), adenocarcinoma (n = 8, 9%) and polyps (n = 5, 5%) (Table 1). Twelve rabbits in the NoUD group had neoplastic findings (13%). Importantly, uteri of 13 rabbits (14%) in the NoUD group were deemed normal on macroscopic examination but exhibited pathological alterations in histology (adenoma n = 2, adenomyosis n = 1, carcinoma in situ n = 1, cystic endometrial hyperplasia n = 8, polyp n = 1). On the other hand, only one of the 23 rabbits less than one year of age exhibited a pathological finding (cystic endometrial hyperplasia). Figs. 1 and 2 exhibit examples of macroscopic alterations in the unopened uterus and histology of uterine adenomata.

In the UD group, 21 (95%) out of 22 rabbits exhibited pathological alterations of the uterus; in 2 (10%) of these, the changes (cystic endometrial hyperplasias) showed only in histology. Only one rabbit, neutered due to a mammary gland tumour, displayed no pathological findings in the uterus. The 21 affected animals showed various pathologies (Table 2). The most frequent diagnoses were cystic endometrial hyperplasia (n = 17, 77%) and adenocarcinoma (n = 12, 54%), 12 rabbits in total (55%) exhibiting neoplasias. The 5 rabbits with reported reproductive problems displayed various pathologies: adenocarcinoma

Table 1
Number of Rabbits With Different Combinations of Pathological Diagnoses Observed in Histological Examination of the Uterus. Only Diagnoses Observed in More Than One Rabbit are Shown in the List

	Adenocarcinoma	Adenomyosis	Cystic endometrial Hyperplasia	Adenoma	Hydrometra	Polyp	Serosal inclusion Cyst
Adenocarcinoma	20	3	17	1	4	2	1
Adenomyosis	3	4	3	0	0	0	0
Cystic endometrial hyperplasia	17	3	41	3	3	5	1
Adenoma	1	0	3	4	0	1	0
Hydrometra	4	0	3	0	5	0	0
Polyp	2	0	5	1	0	7	0
Serosal inclusion cyst	1	0	1	0	0	0	3

Table 2
Number of Rabbits With Different Uterine Disorders Found in Histological Examination of the Uterus Without Any Clinically Suspected Uterine Disease

		N[a]	Macroscopic changes[b]	Source of the sample				Mean age	SD[c]	Range
				Routine neutering		Euthasia/ death				
				Age ≤ 3	Age > 3	Age ≤ 3	Age > 3			
N[a]		**94**		35	20	22	11	2.6	2.1	0.4-10.0
Neoplastic										
	Adenoma	**3**	**2**	1	2	0	1	5.0	2.0	2.8-7.6
	Adenocarcinoma	**8**	**8**	0	1	1	6	6.5	3.0	2.1-10.0.
	Carcinoma in situ	**1**	**0**	1	0	0	0	1.7	NA	NA
	Leiomysarcoma	**1**	**1**	0	1	0	0	7.6	NA	NA
Non-neoplastic										
	Adenomyosis	**2**	**1**	1	0	0	1	5.7	6.0	1.5-10.0
	Cystic hyperplasia	**24**	**16**	4	12	3	5	4.2	2.3	0.7-10.0
	Hydrometra	**2**	**2**	0	0	0	2	6.0	4.1	3.1-8.9
	Polyp	**4**	**4**	1	2	2	0	3.0	0.6	2.3-3.7
	Serosal inclusion cyst	**1**	**1**	1	0	0	0	0.7	NA	NA
	Wolffian duct cyst	**1**	**1**	0	0	0	1	6.9	NA	NA

[a] Number of rabbits. Age missing in 6 cases.
[b] Number of rabbits with abnormal changes in the macroscopic examination of the uterus
[c] Standard devision

(n = 1), granulomatous inflammation (n = 1), hydrometra (n = 1), pyometra (n = 1) and serosal inclusion cyst (n = 1). Two of them also had cystic endometrial hyperplasia.

The mean age of all rabbits (n = 24) with tumours was 6.1 years (SD 2.3, range 1.7–10.0), and the mean age of rabbits with non-tumorous pathologies (n = 28) was 3.5 years (SD 1.6, range 0.7–6.5). Age distribution of all rabbits with cystic endometrial hyperplasia and adenocarcinoma is presented in Fig. 3; the youngest rabbit with cystic endometrial hyperplasia was aged 0.7 years and the youngest with adenocarcinoma 2.1 years. Among all animals with known age (NoUD and UD; n = 110), uterine malignant neoplasia affected 40% of those aged over 3 years and the odds were 19.3-fold (95% CI 4.2-88.3, $P < 0.001$) larger than in those under three years (prevalence 3.3%). In the NoUD group (n = 88), 29.0% of the over three-year-old rabbits showed uterine neoplasia compared with younger animals, in which the prevalence was 5.3% (OR 7.4, 95% CI 1.8–29.8, $P = 0.005$). Neoplastic changes were present in 6 out of 36 (17%) mixed breed rabbits, in 7 of 20 (35%) Dwarf Lops, and in 11 of 60 (18%) combined other breeds. The corresponding prevalences of

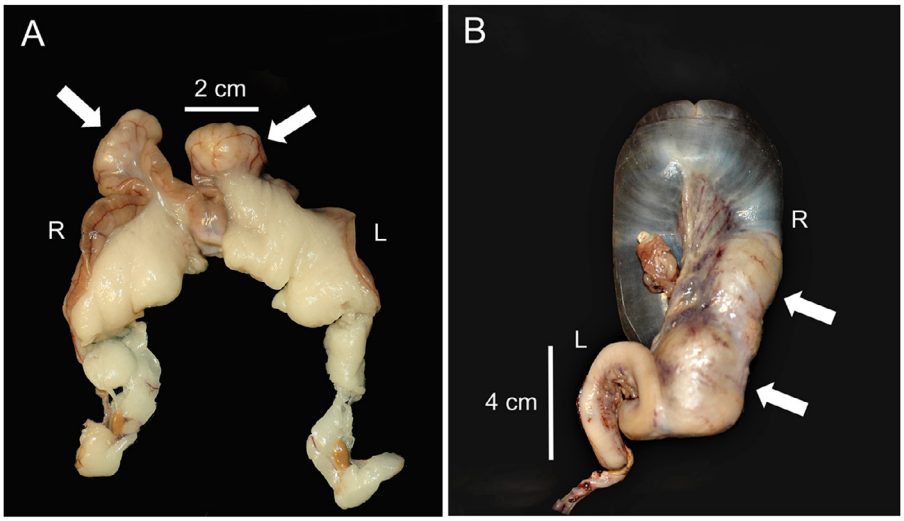

Fig. 1. Examples of uteri with macroscopic alterations, rabbit. (A) Bilateral adenocarcinoma (arrows) and cystic endometrial hyperplasia of the right (R) uterus (uterine horn). (B) Adenocarcinoma (arrows) and hydrometra in the right (R) uterus, cystic endometrial hyperplasia in the left (L) uterus. The cystic endometrial hyperplasias are macroscopically inconspicuous.

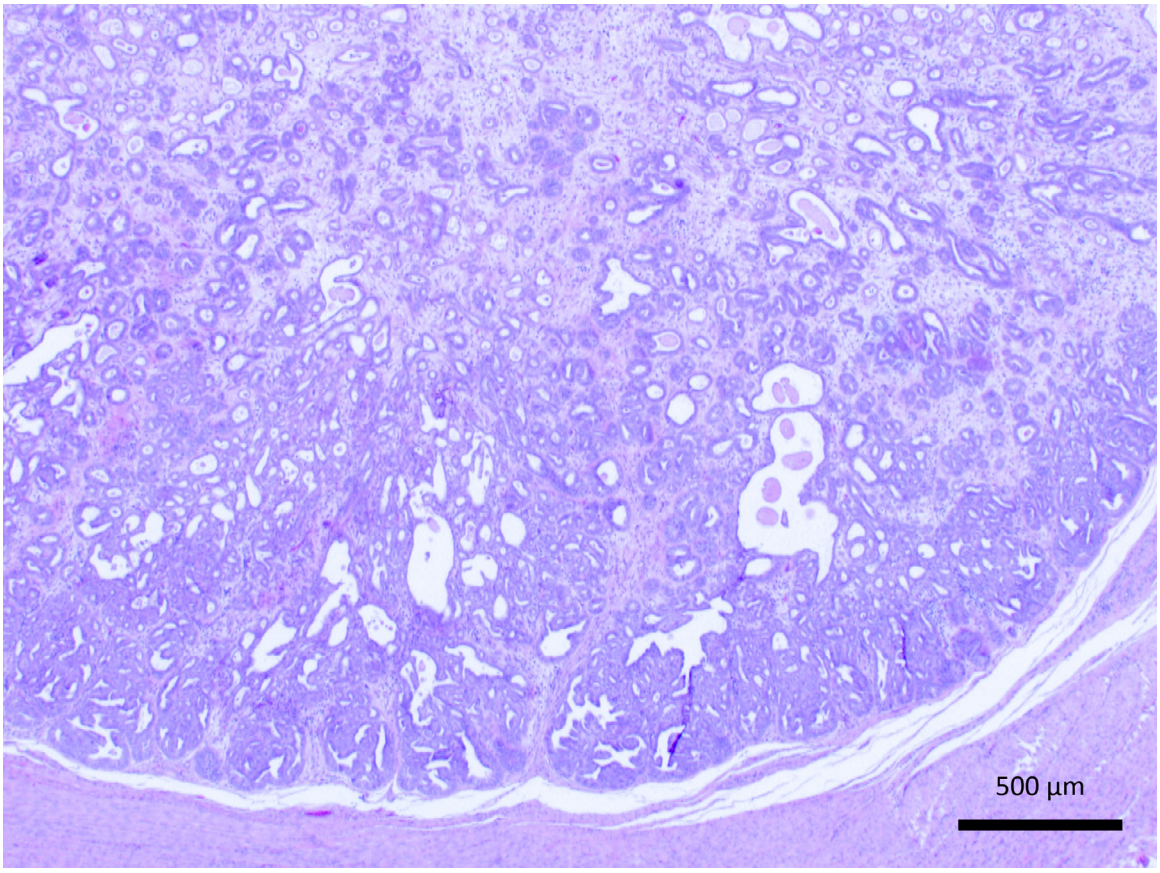

Fig. 2. Uterine adenoma, rabbit. Part of a solitary mass that protrudes into the uterine lumen. Objective magnification 2.5x.

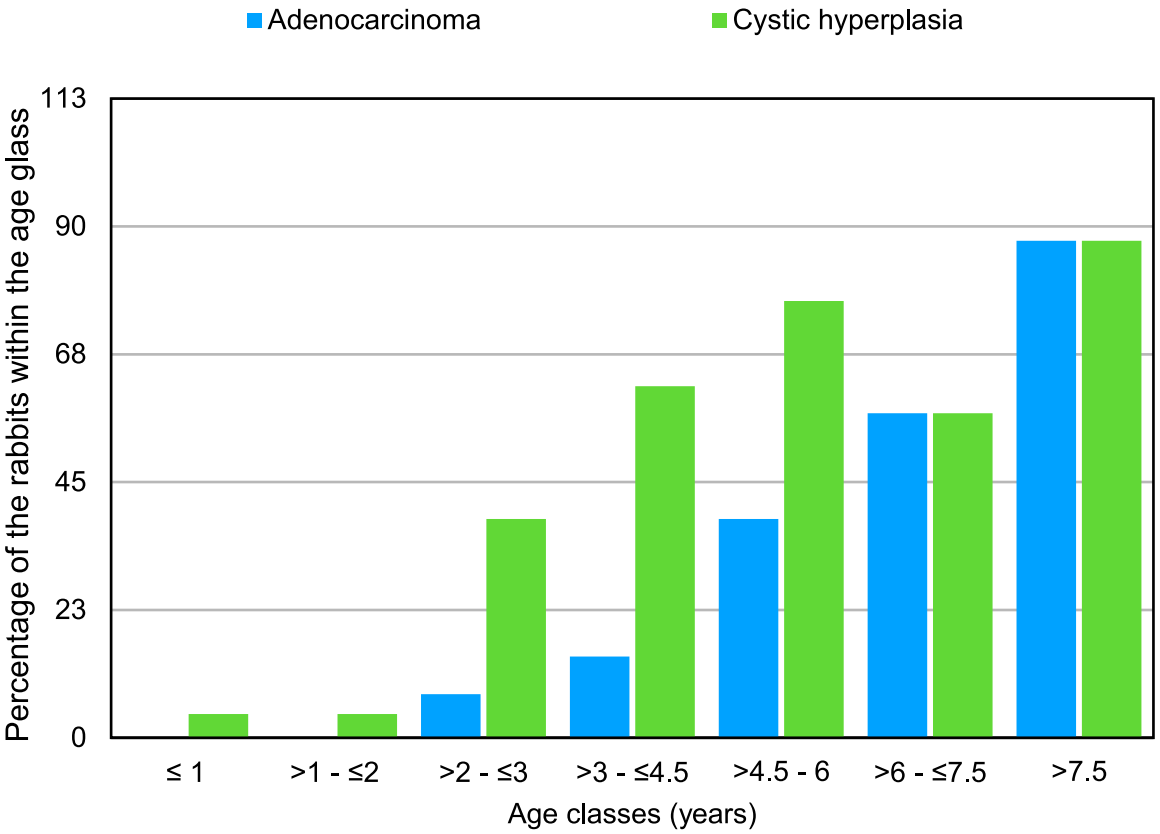

Fig 3. Age distribution of domestic rabbits with uterine adenocarcinoma and cystic endometrial hyperplasia (n = 110). Note that the age period is one year for rabbits under 3 years of age and 1.5 years for older rabbits.

Table 3
Uterine Pathologies Found in 22 Domestic Rabbits With Suspected Uterine Disease

		N[a]	Macroscopic changes[b]	Age ≤ 3 years	Age > 3 years	Mean age, years	SD[c]	Range
N[a]		22		3	19	5.3	2.1	1.5 – 8.7
Neoplastic								
	Adenocarcinoma	12	12	0	12	6.4	1.4	4.1 – 8.7
	Leiomyoma	1	1	0	1	8.7	NA[d]	NA
Non-neoplastic								
	Adenomyosis	2	2	0	2	7.4	0.3	7.2 – 7.6
	Cystic endometrial hyperplasia	17	15	0	17	5.9	1.6	3.1 – 8.7
	Granulomatous inflammation	1	1	0	1	3.1	NA	NA
	Hydrometra	3	3	1	2	5.3	3.5	1.8 – 8.7
	Osseus metaplasia	1	1	0	1	8.0	NA	NA
	Polyp	2	2	0	2	7.1	0.6	6.7 – 7.6
	Pyometra	1	1	1	0	1.7	NA	NA
	Serosal inclusion cyst	2	2	1	1	4.0	3.5	1.5 – 6.4

[a] Number of rabbits. Age missing in 6 cases.
[b] Number of rabbits with abnormal changes in macroscopic examination of the uterus.
[c] Standard deviation.
[d] Not applicable.

non-neoplastic disorders were 15 of 36 (42%) in mixed breed rabbits, 9 of 20 (45%) in Dwarf Lops, and 25 of 60 (42%) in other breeds. Neither neoplastic ($P = 0.249$) nor non-neoplastic ($P = 0.968$) changes exhibited statistically significant breed predilection, albeit the neoplastic changes were noticeable more prevalent in Dwarf Lops than in other the other two breed divisions.

Cystic endometrial hyperplasia was the most common diagnosis in histopathology and was frequently diagnosed with other pathologies (Table 3). It was diagnosed simultaneously with adenocarcinoma in 17 animals, corresponding to 85% of rabbits with adenocarcinoma and 41.5% of rabbits with cystic endometrial hyperplasia. The association was highly significant ($P < 0.001$). Four different uterine disorders (adenocarcinoma, cystic endometrial hyperplasia, hydrometra, leiomyoma) were diagnosed simultaneously in one rabbit. Three simultaneous diagnoses were observed in 12 rabbits, and two in 11 rabbits. Carcinoma in situ, pyometra, granulomatous inflammation, leiomyoma, leiomyosarcoma, and Wolffian duct cyst were all diagnosed once. Carcinoma in situ and pyometra were both diagnosed as sole diagnoses. Granulomatous inflammation was diagnosed together with cystic endometrial hyperplasia. Leiomyoma and Wolffian duct cyst were diagnosed simultaneously with adenocarcinoma and cystic endometrial hyperplasia. A rabbit with leiomyosarcoma also had cystic endometrial hyperplasia and adenoma. All other findings were diagnosed in several rabbits, and the combinations of diagnoses are shown in Table 3.

Discussion

We report the prevalence of uterine pathologies in rabbits of various ages neutered, deceased or euthanized without a suspected uterine disease and in rabbits neutered or euthanized due to a suspected uterine disease. The results of this study of uterine disorders in 116 domestic rabbits show that over 40% of rabbits without the suspected uterine disease had pathological findings in the histopathological examination. Tumours were diagnosed even in rabbits undergoing routine neutering and 11% of rabbits in NoUD group had a malignant tumour that could potentially develop the life-threatening disease.

We also compared the results between macroscopic and histopathological examinations. Almost 14% of NoUD uteri assessed as macroscopically normal had pathological findings in histopathological examination. Two of these findings were neoplastic (one malignant) and were present in rabbits aged under three years. Divers [20] recommended carefully evaluating the uterus before (laparoscopic) ovariectomy, and prefer ovariohysterectomy if any abnormal tissue is visible. Regarding the results of our study, the macroscopic evaluation does not fully exclude pathology in the rabbit uterus and even malignant pathologies may be missed without histopathological examination. Therefore, ovariohysterectomy should be recommended. Concurrently, in healthy dogs and cats, which generally exhibit a low incidence of uterine tumours [21,22], ovariectomy has become the procedure of choice for neutering, albeit ovariohysterectomy has also been advocated for the prevention of reproductive pathologies [22]. Some concern has been expressed about the possible progression of subclinical uterine disorders after ovariectomy in rabbits, as follow-up research in this area has thus far been lacking [23]. An earlier study of oestrogen and progesterone receptors in the endometrium of pet rabbits revealed two different types of adenocarcinomas with different receptor expressions [24]. Tubular/solid adenocarcinomas maintained both oestrogen and progesterone receptors, whereas papillary adenocarcinomas (the most common type of adenocarcinoma in the study) lost the expression of both receptors in the early stage of their development, suggesting that oestrogen and progesterone may not be vital for the progression of all types of adenocarcinomas. In contrast, in the same study, over 80% of samples with cystic endometrial hyperplasia were oestrogen receptor-positive, suggesting that this hormone plays a major role in the development of cystic endometrial hyperplasia. According to Divers [20], ovariectomy should be performed on only very young rabbits (under 6 months of age). The Rabbit Welfare Association and Fund (RWAF) and the British Veterinary Zoological Society (BVZS) recommend early neutering (at age 3–6 months) for all pet rabbits [10].

The previously reported high risk of uterine disorders, especially neoplastic ones, in rabbits has recently been questioned [6,11]; the author suggested a prevalence of 3–4% for adenocarcinoma in the macroscopic examination of uteri in rabbits undergoing routine neutering and 10-13% in abdominal palpation of rabbits aged 5 years or more at time of death. This is in stark contrast to our results indicating adenocarcinoma prevalence of 9% and all neoplasia prevalence of 13% in the NoRD group (mean age 2.6 years), with corresponding prevalences of 55% and 59% in the RD group (mean age 5.3 years). As some of the neoplasia (adenoma, carcinoma in situ) were missed even with macroscopic examination of the uteri, they surely would be missed if only palpation is used to determine abnormalities of the rabbit uterus. Palpation is an unreliable method for distinguishing between non-neoplastic and neoplastic abnormalities. Recently, whole-body radiographs were reported to be one possible method for detecting uterine disorders in rabbits [25]. Histopathological examination should be, however, preferred for final diagnosis.

Cystic endometrial hyperplasia and adenocarcinoma were the most common pathological findings in rabbits of our study, in accord with previous reports [13,14,16]. However, we recorded no senile atrophy of the endometrium or pregnancy toxaemia, both of which have been

associated with adenocarcinoma in rabbits. Notably, senile atrophy of the endometrium and pregnancy toxaemia are associated with glandular hyperplasia in humans [26,27]. Our results are consistent with earlier studies [14,24,27] that have reported that adenocarcinoma can develop independently, as three rabbits with adenocarcinoma in our study did not have cystic hyperplasia. Furthermore, 27 rabbits had previously been pregnant, 7 of which had a uterine disorder. Although the sample size was small, pregnancy did not appear to be associated with uterine disorders in our rabbit population.

Small litters, stillborn kits, and infertility were signs reported as reproductive problems, and all of these rabbits showed uterine disorders. These results are in agreement with previous reports of infertility, reduced litter size, and dead kits being initial signs of uterine tumours [26]. However, Greene and Saxton [26] reported these initial signs at least 4–6 months prior to detection of the tumours in abdominal palpation. These signs should therefore be kept in mind as a possible sign of uterine disorder in breeding rabbits. In pet rabbits not used for breeding, these initial warning signs are missed and uterine disorders may be noticed much later.

This study has some limitations. The sample size was smaller than we planned despite the study being actively advertised. Routine neutering of female rabbits is not common in Finland; only 26% of female rabbits participating in an intestinal parasite prevalence study (unpublished data [28]) and 14% of female rabbits participating in a health survey [19] were neutered. In comparison, 51% of female rabbits were neutered in a British study [29]. As Rabbit Haemorrhagic Disease and myxomatosis were not present in Finland during this study, rabbits did not come to veterinary clinics for regular health check-ups where neutering could be advised. Many rabbits were neutered after they visited veterinary clinics later in life due to a health issue and spaying was recommended. At that stage, the rabbits are usually older and may have findings on abdominal palpation. Some samples might have been missed due to mistakes and oblivions, as the collaborating veterinarians were helping with the project on a voluntary basis alongside their daily work, and some of the owners may have refused to participate. The number of these cases is unknown. As we collected uteri from rabbits neutered, died, or euthanized, we were unable to study pregnancy-related uterine disorders. Finally, we have no detailed knowledge of the diagnoses or diagnostic methods employed by the collaborating veterinarians for those rabbits (n = 8) the veterinarians deemed to have a uterine disease.

Conclusions

Our results indicate that uterine disorders are common in domestic rabbits. Uterine abnormalities were present in 44% and neoplasia in 13% of rabbits without the suspected uterine disease. Uterine malignant neoplasia affected 40% of all rabbits aged over three years, and the odds of a malignant uterine tumour in these rabbits were approximately 19-fold higher than in rabbits aged under three years. However, pathologies may be present in rabbits as young as 1–2 years. A macroscopically normal uterus may have pathological changes and ovariohysterectomy should be therefore preferred over ovariectomy at least in older rabbits.

CRediT author statement

Johanna Mäkitaipale: conceptualization, investigation, resources, writing - original draft & review & editing, *Niina Airas:* conceptualization, methodology, investigation, resources, supervision, writing - original draft & review & editing, *Sanna Engblom:* investigation, resources, formal analysis, writing - original draft, *Jere Lindén:* conceptualization, methodology, formal analysis, writing - original draft & review & editing

Acknowledgements

This research did not receive any grants from funding agencies in the public, commercial or non-profit sectors. We thank colleagues, rabbit breeders and owners for providing the samples.

Conflict of interest statement

None of the authors has any financial or personal relationships that could inappropriately influence or bias the content of the paper.

References

[1] Polson CJ. Tumours of the rabbit. J Pathol Bacteriol 1972;30:603–14.
[2] Orr JW, Polson CJ. Uterine cancer in the rabbit. Am J Cancer 1938;32:114–25.
[3] Greene HSN. Uterine adenomata in the rabbit III. Susceptibility as a function of constitutional factors. J Exp Med 1941;73:273–92.
[4] Heatley J, Smith AN. Spontaneous neoplasms of lagomorphs. Vet Clin North Am Exotic Pract 2004;7:561–77.
[5] Bertram CA, Müller K, Klopfleisch R. Genital tract pathology in female pet rabbits (*Oryctolagus cuniculus*): a retrospective study of 854 necropsy examinations and 152 biopsy samples. J Comp Pathol 2018;164:17–26.
[6] Whitehead ML. '80% of entire female rabbits get uterine adenocarcinoma.'A case report of a veterinary factoid. In: Proceedings of the British Veterinary Zoological Society conference; 2015.
[7] Bradbury AG, Dickens GJE. Should we advocate neutering for all pet rabbits? Vet Record 2016;179:654–5.
[8] Harcourt-Brown F. Neutering of pet rabbits. Vet Record 2017;180:385–6.
[9] Saunders R. Neutering of pet rabbits. Vet Record 2017;180:77.
[10] Saunders R, Stidworthy M. Neutering of pet rabbits. Vet Record 2017;180:77.
[11] Whitehead ML. Neutering of pet rabbits. Vet Record 2017;180:204–5.
[12] Harcourt-Brown FM. Disorders of the reproductive tract of rabbits. Vet Clin North Am Exotic Pract 2017;20:555–87.
[13] Saito K, Nakanishi M, Hasegawa A. Uterine disorders diagnosed by ventrotomy in 47 rabbits. J Vet Med Sci 2002;64:495–7.
[14] Walter B, Poth T, Böhmer E, Braun J, Matis U. Uterine disorders in 59 rabbits. Vet Record 2010;166:230–3.
[15] Reimnitz L, Sanchez-Migallon Guzman D, Alex C, Summa N, Gleeson M, Cissell DD. Multiple endometrial venous aneurysms in a domestic rabbit (*Oryctolagus cuniculus*). J Exotic Pet Med 2017;26:230–7.
[16] Künzel F, Grinninger P, Shibly S, et al. Uterine disorders in 50 pet rabbits. J Am Anim Hosp Assoc 2015;51:8–14.
[17] Baum B. Not Just Uterine Adenocarcinoma-Neoplastic and Non-Neoplastic Masses in Domestic Pet Rabbits (*Oryctolagus cuniculus*): A Review. Vet Pathol 2021;58:890–900.
[18] Bertram CA, Bertram B, Bartel A, et al. Neoplasia and Tumor-Like Lesions in Pet Rabbits (*Oryctolagus cuniculus*): A retrospective analysis of cases between 1995 and 2019. Vet Pathol 2021;58:901–11.
[19] Mäkitaipale J, Harcourt-Brown F, Laitinen-Vapaavuori O. Health survey of 167 pet rabbits (*Oryctolagus cuniculus*) in Finland. Vet Record 2015;177:418.
[20] Divers SJ. Clinical technique: Endoscopic oophorectomy in the rabbit (*Oryctolagus cuniculus*): The future of preventative sterilisations. J Exotic Pet Med 2010;19:231–9.
[21] Miller MA, Ramos-Vara JA, Dickerson MF, et al. Uterine Neoplasia in 13 Cats. J Vet Diagn Invest 2003;15:515–22.
[22] Maya-Pulgarin D, Gonzalez-Dominguez MS, Aranzazu-Taborda D, Mendoza N, Maldonado-Estrada JG. Histopathologic findings in uteri and ovaries collected from clinically healthy dogs at elective ovariohysterectomy: a cross-sectional study. J Vet Sci 2017;18:407–14.
[23] Harcourt-Brown F. Neutering. In: Harcourt-Brown F, Chitty J, editors. BSAVA Manual of Rabbit Surgery, Dentistry and Imaging. 1st Edn. Gloucester: British Small Animal Veterinary Association; 2013. p. 138–56.
[24] Asakawa MG, Goldschmidt MH, Une Y, Nomura Y. The immunohistochemical evaluation of estrogen receptor- and progesterone receptors of normal, hyperplastic, and neoplastic endometrium in 88 pet rabbits. Vet Pathol 2008;45:217–25.
[25] Lübke VC, Fehr M, Köstlinger S. Validation of whole-body radiographs for examining uterine disorders in sexually intact female rabbits. Tierarztl Prax Ausg K Kleintiere Heimtiere 2019;47:14–24.
[26] Greene HSN, Saxton JA. Uterine adenomata in rabbit I. Clinical history, pathology and preliminary transplantation experiments. J Exp Med 1938;67:691–715.
[27] Baba N, von Haam E. Animal Model: Spontaneous Adenocarcinoma in Aged Rabbits. Am J Pathol 1972;68:653–6.
[28] Mäkitaipale J, Karvinen I, Virtala A-MK, Näreaho A. Prevalence of intestinal parasites and risk factor analysis for *Eimeria* infections in Finnish pet rabbits. Vet Parasitol 2017;9:34–40.
[29] Rooney NJ, Blackwell EJ, Mullan SM, et al. The current state of welfare, housing and husbandry of the English pet rabbit population. BMC Res Notes 2014;7:942.