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Authors: Stott, Philip, and Wight, Nicole

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FEMALE REPRODUCTIVE TRACT ABNORMALITIES IN EUROPEAN HARES (*LEPUS EUROPAEUS*) IN AUSTRALIA

Philip Stott[1,2] and Nicole Wight[1]

[1] Department of Animal Science, University of Adelaide SA 5005, Australia and Pest Animal Control Cooperative Research Centre, GPO Box 284, Canberra ACT 2601, Australia

[2] Corresponding author (email: philip.stott@adelaide.edu.au)

ABSTRACT: Populations of European hare (*Lepus europaeus*) are in decline in Europe, and populations in Australia remain at low densities. Populations are sensitive to size of the breeding stock, which is influenced by fertility in the females. From 1996 to 1999, a total of 272 adult female hares from three Australian populations were dissected and their reproductive systems examined for abnormalities. Cystic endometrial hyperplasia was relatively common and often accompanied by hydrosalpinx. Extrauterine fetuses, neoplasms, pseudopregnancies, and resorptions also were found. However, although pseudopregnancies and resorptions were found in young adults (<12 mo) as well as older hares, conditions possibly causing infertility were almost always in older hares with prevalences up to 46.2%. Only hares with access to known sources of estrogens exhibited pathologic conditions, but sympatric European rabbits (*Oryctolagus cuniculus*) did not, which is consistent with known difference in responses between the corpora lutea of the two species to exogenous estrogen. Infertility at such a high prevalence could compound and extend the impact of years of low juvenile survival on recruitment.

Key words: European hare, European rabbit, fertility, *Lepus europaeus, Oryctolagus cuniculus,* phytoestrogen.

INTRODUCTION

In recent years there has been considerable concern about an apparent decline in populations of European hare (*Lepus europaeus*) in western and central Europe where it is an important game animal (Homolka and Zima, 1999). Populations in Australia are also at low densities due to unknown factors despite a history of plague densities and considerable environmental and economic losses in some regions (Douglas, 1972) since its introduction from England (Rolls, 1969). The hare is sympatric with European rabbit (*Oryctolagus cuniculus*) in many areas of Europe, South America, New Zealand, and Australia (Chapman and Flux, 1990).

Although it has a potential life span in the wild of 13 yr (Broekhuizen, 1979), the mean life span of adult hares (reviewed by Marboutin and Peroux, 1995) is about 2.5 yr. Jills reach sexual maturity at 6–7 mo and can breed in their first year of life (Broekhuizen and Maaskamp, 1981). Recruitment into the population is influenced by the number of breeding jills, the number and sizes of litters each jill produces in a breeding season, and survival rate of leverets (Hansen, 1992). Growth rate of the population is sensitive to survival of the breeding stock if recruitment is weak (Marboutin and Peroux, 1995). Hence, factors that remove older jills from the breeding stock can be critical in determining whether hare populations will increase or decrease in density. Both mortality and infertility can remove animals from the breeding stock, with the impact of infertility greater in populations with high birth rates and high mortality (Barlow et al., 1997), such as the hare. In our study, the prevalence and expression of reproductive abnormalities in adult jills in Australia were investigated.

MATERIALS AND METHODS

Hunters submitted carcasses of jills shot on the Volcanic Plains of western Victoria (centered at 37°50′S, 142°04′E), the Monarto Plains of South Australia (35°14′S, 139°05′E), and the Chowilla Floodplain of South Australia (33°59′S, 140°55′E), in each month of the year from 1996 to 1999. The Volcanic and Monarto Plains are both agricultural regions with pastures comprising grasses mixed with legumes such as medic and clover; the Monarto Plains also has extensive areas of leguminous crops such as lupins, soy bean, and vetch; and the

TABLE 1. Results of examination of female European hares (jills) and rabbits (does) from three regions in Australia for reproductive condition and abnormalities, 1996–99.

	Chowilla floodplain		Monarto plains		Volcanic plains		Other jills	Total	
	Jills	Does	Jills	Does	Jills	Does		Jills	Does
Total adult females	41	24	72	22	130	34	2	245	80
Age 6–12 mo	15	9	24	21	66	19	1	106	49
Age >12 mo	19	15	39	1	38	15	1	97	31
No lens	7	—	9	—	26	—	—	42	—
Pregnant	22	22	29	14	59	18	—	110	54
Age 6–12 mo	6	8	11	13	32	10	—	49	31
Age >12 mo	9	14	13	1	17	8	—	39	23
No lens	6	—	5	—	10	—	—	21	—
Abnormalities[a]	5	2	24	2	21	—	1	51	4
Age 6–12 mo	—	1	3	2	1	—	—	4	3
Age >12 mo	4	1	20	—	15	—	1	40	1
No lens	1	—	1	—	5	—	—	7	—
Infertile[a]	—		23		14		1	38	
Age 6–12 mo	—		3		—		—	3	
Age >12 mo	—		18		10		1	29	
No lens	—		1		4		—	5	

[a] See text for discussion of the abnormalities observed in these animals.

Chowilla Floodplain is a region of natural vegetation, lacking crops and pastures. The carcasses were aged according to the dried eye lens method of Suchentrunk et al. (1991) and divided into age classes. Hares younger than 6 mo were classed as juveniles and not included in this study. Adults were divided into two classes, 6–12 mo and >12 mo. The abdominal cavity was opened by reflecting the left flank, and organs were inspected in situ before removal. The reproductive tract was transected just caudad to the cervix and removed, and the oviducts were inspected visually before the ovaries were separated and preserved in formalin for later examination. Visual inspection of the ovaries was done by examination of serial sections taken at 1.0-mm intervals. The uterine horns were opened while fresh and visually inspected for macroscopic indications of pregnancy or of reproductive abnormalities. Representative tissue samples from eight uteri, two ovaries, two oviducts, and one mammary gland were preserved in 10% buffered formalin, and later sectioned and stained with nematoxylin and eosin for histopathologic examination.

When lesions were found in the reproductive tracts of the jills, samples of adult female rabbits (does) were obtained from the same regions and in most cases from the same properties, and they were processed in the same manner as the hares using the equivalent eye lens aging technique for rabbits (Myers and Gilbert, 1968). Does <6 mo of age (juveniles) or those for which no eye lens was available were excluded from further consideration.

The data were analyzed using log-linear model testing for a relationship between abnormalities and the explanatory factors of population (Volcanic Plains, Monarto Plains, and Chowilla Floodplain) and age (younger adult female and older adult female) using GenStat 6th edition (Lawes Agricultural Trust, Harpenden, Hertfordshire, UK).

RESULTS

Reproductive abnormalities were found in 20.8% (51/245) of the jills examined (Table 1). Thirty-three jills exhibited macroscopically visible lesions in the uterus. Abnormalities included multiple opalescent cysts of variable diameter up to 7 mm distributed throughout the uterine horns (Fig. 1), which were diagnosed as cystic endometrial hyperplasia (25 cases); the presence of translucent mucoid fluid in the uterus in conjunction with one or more large corpus luteum, which was diagnosed as pseudopregnancy (2); the presence of opaque yellowish fluid containing

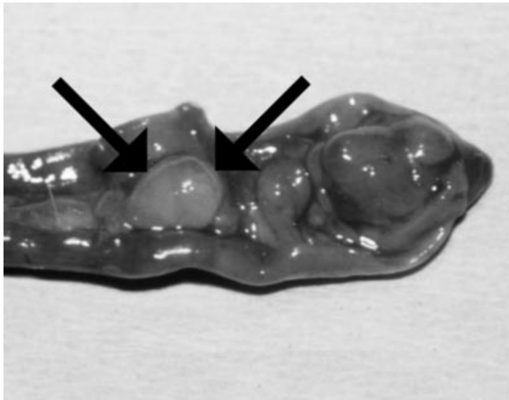

FIGURE 1. Opened tip of uterine horn of a female European hare from Australia. Arrows indicate a prominent thin-walled endometrial cyst, but many thicker walled cysts are also visible.

small flecks of darker, more solid material and with an unpleasant odor, which was diagnosed as endometritis (2); the occurrence of multiple, circumscribed, raised, and distinctly red areas in the endometrium, <2 mm in size, distributed throughout the uterine horns, which was called focal endometrial venous congestion based on histologic appearance (2); and presence of thickening (>2 mm) of the muscularis of the wall of the uterus, which cut crisply with scissors, which was termed myometrial thickening and fibrosis (2). Twelve of these 33 (but not including the pseudopregnant animals) also had lesions in the oviduct(s), and another four animals had lesions in the oviduct(s) but not in the uterus.

Oviduct abnormalities appeared macroscopically as distensions mostly with opalescent but sometimes with purulent or bloodstained fluid (Figs. 2, 3), which was unilateral in five jills and bilateral in 11 jills. None of the 37 jills with uterine and/or oviduct lesions was pregnant, and they were judged to be at least temporarily infertile. Hares with lesions consistent with infertility contributed only a portion of the total reproductive tract abnormalities listed in Table 1.

Ovaries were available for 32 of the 37 jills with uterine or oviduct lesions. Corpora lutea were found in ovaries from 20 jills (including both cases of pseudopregnancy), two had corpora hemorrhagica, six had follicles, and four had no visible sign of activity.

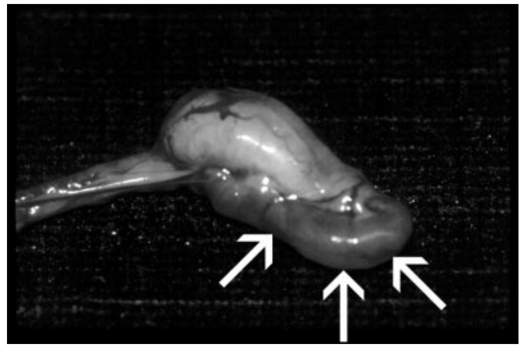

FIGURE 2. Ovary of a female European hare from Australia showing grossly distended oviduct (arrows).

Hares judged to be infertile and for which eye lens data were available represented 29.9% of all female hares >12 mo but only 2.8% of those 6–12 mo. In older jills, lesions consistent with infertility were recorded in all months. Prevalence of presumed infertility was 46% in the Monarto Plains population and 26.3% in the Volcanic Plains population, but none of the 19 older females in the Chowilla Floodplain population was judged to be infertile. The combined data for all jills from the Monarto and Volcanic Plains sites are presented as Figure 4.

Reproductive abnormalities not neces-

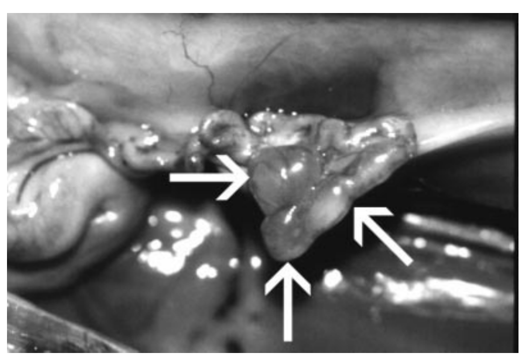

FIGURE 3. In situ view of uterus (left) and broad ligament (above) of a female European hare from Australia showing acinose oviduct (arrows).

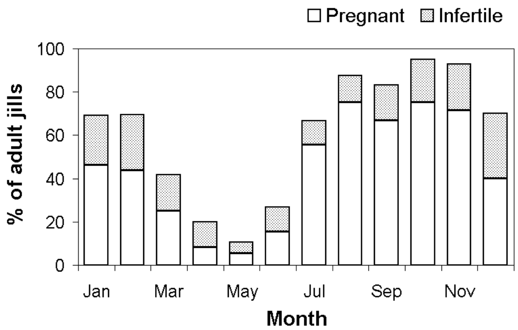

FIGURE 4. Combined prevalence of visible pregnancy and infertility by month in adult female European hares from the Monarto and Volcanic Plains, Australia.

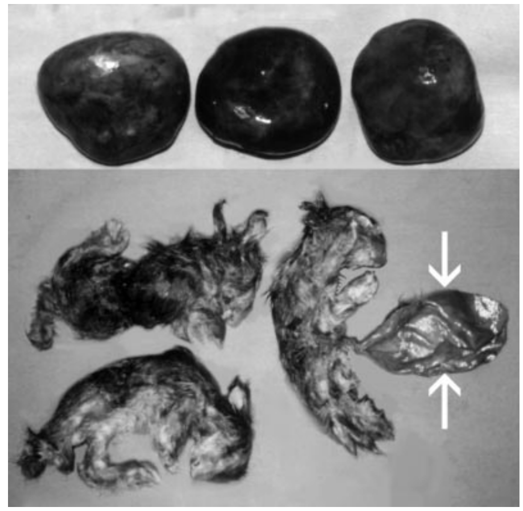

FIGURE 5. Three spheroid masses (above) containing three mummified fetuses (below) removed from the peritoneal cavity of a female European hare from Australia. Between arrows is the bounding membrane of one mass, showing an umbilical connection to the fetus.

sarily related to fertility were also observed in some jills (Table 1). One jill had two completely macerated fetuses in one horn and a single apparently normal fetus at 38 days gestation in the other; cysts were observed in the ovary of two animals; masses occurred in the uterus and/or broad ligament in three animals and the mammary gland of another animal; four jills had adhesions involving reproductive organs; and two had extrauterine mummified fetuses contained within intact fetal membranes (Fig. 5). One of the jills with extrauterine fetuses also had bilateral salpingitis, the jill with a mammary mass also had cystic endometrial hyperplasia, and a jill with cystic ovaries also had a severe case of cystic endometrial hyperplasia involving the myometrium, hydrosalpinx, and adhesions between the uterus, parietal peritoneum, and intestines. Resorbing fetuses were found in 11 uteri, in six instances of which only a portion of the litter was affected, and in one oviduct. No seasonal trend in resorption was obvious, but four cases were from the Chowilla Floodplain. With the exception of one animal with adhesions and two cases of resorption, all of these hares for which eye lenses were available were >12 mo old. Both the interactions between abnormalities (excluding resorption) and population and between disease and age were significant ($P<0.001$) at the 5% level, with a significantly higher proportion of the older adult females (52.4%) being abnormal compared with the younger adult females (4.0%) and a significantly higher proportion of the Monarto Plains hares being abnormal (37%) compared with the Volcanic Plains hares (13.7%) and the Chowilla hares (0%).

Few reproductive abnormalities were observed in the does (Table 1). Two instances of partial reabsorption occurred, one in a young doe and the other in an older doe. There was also one case of multiple, circumscribed, raised, and distinctly red areas in the endometrium, <2 mm in size, distributed throughout the uterine horns, in a young doe. The only other abnormality involved a young doe bearing a litter with an overdeveloped (fully furred) fetus of 43 g, and two fetuses of 19 and 16 g with reduced numbers of digits (1–3) one of which had incomplete fusion of the abdominal cavity out of which a portion of the liver protruded.

Microscopically, uteri with endometrial cysts contained clear fluid and dilated glands with minimal leukocytic infiltration, whereas uteri with opaque fluid had re-

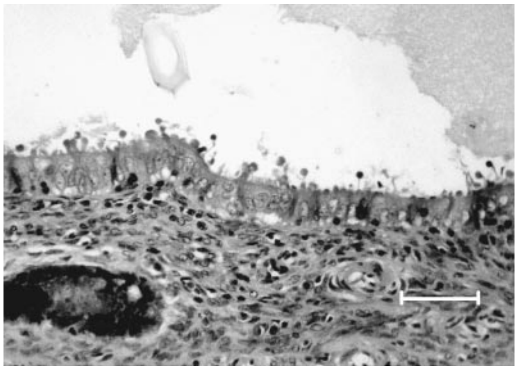

FIGURE 6. Photomicrograph of section of a distended oviduct of a female European hare from Australia showing protoplasmic extrusions from the epithelial surface, many with attenuated peduncles, and the presence of free globules in the lumen. Hematoxylin and eosin staining. Bar=50 μm.

duced numbers of dilated glands with significant lymphoplasmacytic and polymorphonuclear leukocytic infiltration. Cysts were lined with greatly attenuated epithelium. Distended oviducts were lined with a monolayer of ciliated cuboidal to low columnar and attenuated epithelium within the same tube, and there were many pedunculated protoplasmic extrusions into the lumen from the ciliated surface that became increasingly attenuated before being released as globules (Fig. 6). Ovarian cysts were of various sizes and lined with cuboidal, columnar, or attenuated epithelium within the same ovary. The masses were an organizing hematoma on the serosal surface of one uterus, a leiomyoma within the wall of another, multiple polypous lipomas in the wall of the uterus and on the broad ligament of the third, and a squamous cell carcinoma in the mammary gland.

Focal endometrial venous congestion was characterized by papilliform projections scattered uniformly over the endometrium and consisting of endometrium and associated stroma projecting into the lumen of the uterus. The projections contained markedly congested and closely apposed thin-walled blood vessels with little sign of associated inflammation.

DISCUSSION

Many of the lesions described in this paper have been described in other hare populations but generally as isolated cases. Bensinger et al. (2000) and Hackländer et al. (2001) observed similar pathologic changes in uteri of >12-mo-old European hares in Germany, but apparently they did not examine the oviducts. Focal endometrial venous congestion in our hares was similar to the endometrial venous aneurysms described in rabbits by Bray et al. (1992), but in the hares the distension of the vessels was not as great and no thrombi were present. Tubal lesions were reported by Pépin (1989) in hares from France. In their study, as in ours, the dominant form of abnormality was cystic endometrial hyperplasia. However, the prevalence of lesions in oviducts and uterus may mean that the abnormalities share a common etiologic agent or agents.

Extrauterine fetuses arising through uterine rupture sometimes occur at the time of parturition in a range of species; but spontaneous rupture with subsequent survival of the mother in the absence of medical intervention is a rare phenomenon, which has been recorded in humans (Bannerman, 1965) and sheep (Dennis, 1966). In the hare, however, there are at least seven reports, several of which record more than one instance of this condition (Flux, 1967; Broekhuizen and Maaskamp, 1981). A survey of 416 adult female British hares included a >12-mo-old jill with five extrauterine near full term fetuses and one intrauterine fetus at about midgestation, and another >12-mo-old jill with a single extrauterine fetus (N. Vaughan, pers. comm.). This may mean that hares are particularly prone to the condition but are not necessarily infertile.

Cystic ovarian tumors seem to be relatively common in hares, and tumors of the mammary gland and uterus also have been reported (Flux, 1965). Fetal resorption is not regarded as a disease condition in lagomorphs since it occurs in response to social (Mykytowycz, 1960) or environmental (Hewson, 1976) stress, and it was excluded from the statistical analysis for this reason. Like the jills from the Chowilla Floodplain, hares feeding on natural vegetation in Argentina had no reproductive abnormalities (Bonino and Montenegro, 1997). Thus, in these studies, old female hares in agricultural areas exposed to and feeding on crops and pastures suffered from a suite of reproductive problems, but young female hares and hares feeding on natural vegetation of rangelands did not. Although the etiologic agent(s) for the above conditions are not known, a circumstantial case can be made that they are due to external estrogenic influence. The farms of the Monarto and Volcanic Plains have mixed pastures including legumes known to produce phytoestrogens and mycoestrogens (Reed, 2001), and the Monarto farms also have leguminous crops such as lupins, soybeans, and vetch. In both areas agricultural chemicals are used, some of which are known to have estrogenic activity (Jobling et al., 1995). The hares on the Chowilla Floodplain, on the other hand, have little access to introduced pasture plants, none to crops, and there is no use of agricultural chemicals in the area. Hence, there may be an association between the level of potential exposure to environmental estrogens and the prevalence of infertility in hares. Further, most of the conditions described above have been shown to have some relationship to estrogenic stimulation. Cystic endometrial hyperplasia is the major indication of phytoestrogenism in sheep (Bennetts et al., 1946). Hares are particularly sensitive to the luteotrophic effect of exogenous estrogen, which can double the length of pseudopregnancy in that species (Caillol et al., 1986, 1989). The formation of secretory cells in the oviducts can be induced by exogenous estrogen (Fredricsson, 1959 cited by Odor et al., 1989).

Although hares with uterine rupture are not necessarily infertile, association between this condition and estrogenic compounds have been made. Uterine rupture in humans has been associated with in utero exposure to diethylstilbestrol (Adams et al., 1989) and in sheep with exposure to phytoestrogens (Dennis, 1966). Bennetts et al. (1946) provided a connection between exposure to phytoestrogens and uterine rupture by demonstrating that cystic development of the glands can extend through the full thickness of the myometrium to the extent of causing spontaneous rupture in nonpregnant sheep. Welshons et al. (1987) reported that phytoestrogens can stimulate growth of human mammary neoplasia. Fibrosis of the wall of the uterus in response to exposure to stilbestrol diproprionate has been reported in the bitch (Dow, 1958). Resorption in rabbits may be attributable to stress (Mykytowycz, 1960; Hewson, 1976) but also is associated with use of estradiol implants (Dunsmore, 1971). The least severe reproductive alteration, pseudopregnancy, occurred in young adults. More severe impacts occurred in older adults as expected; Underwood and Shier (1951) demonstrated that the effect of phytoestrogens on sheep became progressively more severe with longer exposure, and Schinckel (1948) showed that the effect is persistent.

Absence of comparable abnormalities in sympatric rabbits strengthens the implication of exogenous estrogens as the etiology of reproductive abnormalities in the hares. Adams et al. (1981) demonstrated that the phytoestrogenic syndrome in sheep involves extension of the life of the corpus luteum in a proportion of ewes and therefore prolongation of the influence of progesterone and resultant pathologic changes. In the rabbit, exogenous estrogens do not prolong the life of the corpus luteum (Miller and Keynes, 1976), whereas they do in hares (Caillol et al., 1989). Hence, the presence of lesions in hares exposed to phytoestrogens but not in sympatric rabbits is consistent with our observations.

If the lesions described in hares in this paper are associated with exposure to exogenous estrogens, the geographic distribution of similar lesions in hares leads us to believe that the syndrome is widespread. Depending upon its prevalence in any particular population, the syndrome is potentially important to hare populations. Recruitment failures may occur in some years due to a sequence of unfavorable weather events (Meriggi and Alieri, 1989) such that few juvenile females are available to breed, and the older jills, which normally make a greater contribution to recruitment than females in their first year (Flux, 1967) because of their longer breeding season and greater mean litter size (Frylestam, 1980), would not be able to compensate. In the year following a recruitment failure, surviving females would be older and prone to infertility, extending the impact of the adverse weather on the population.

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