Received: 19 September 2017 | Accepted: 2 December 2017

DOI: 10.1111/ahe.12335

ORIGINAL ARTICLE

WILEY ANATOMIA HISTOLOGIA EMBRYOLOGIA

Comparative histomorphological study of endometrium in mares

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Summary

Uterine acute post-breeding inflammation is a physiological tissue response to the entry of exogenous elements, with persistent endometritis being the main pathology responsible for subfertility in the mare (*Equus ferus caballus*; Linnaeus, 1758). Mares can be classified as *susceptible* or *resistant* to endometritis according to their ability to remove intrauterine fluid within 48 hr after experimental inoculation. Endometrial biopsy is a technique that is commonly used to establish the degree of lesions that can affect the fertility of the mare. Endometrial histomorphometry is an objective and highly precise diagnostic method. The aim of this study was to compare, during oestrus, the endometrial histomorphometry of mares previously classified as susceptible (SM) or resistant (RM) to endometritis. Endometrial biopsies from 24 mares at the oestrus phase of the cycle were obtained. For the histomorphometric analysis, samples were histologically processed and subjected to routine Haematoxylin–Eosin staining. For the evaluation, the variables were considered as follows: 1-Height of the lining and glandular epithelia (Lining SM = 15.9 μm vs. RM = 13.3 μm; Glandular SM = 15.0 μm vs. RM = 13.0 μm); 2-Perpendicular diameters of endometrial glands (SM = 51.3 μm vs. RM = 44.8 μm); 3-Number of endometrial glands per field (SM = 24.8 glands/field vs. RM = 20.5 glands/field). The results from this study suggest the existence of a relationship between the studied characteristics and the susceptibility/resistance to post-breeding endometritis in mares. Thus, increased epithelial height, greater glandular density and greater development of the glands during oestrus would be related to a higher susceptibility to endometritis.

1 | INTRODUCTION

The endometrium is composed of an epithelial layer and a lamina propria. The epithelial layer or luminal epithelium consists of a single row of cells ranging from low cubic to tall cylindrical cells, either ciliated or secretory, depending on the stage of the oestrous cycle; below this layer, the basement membrane separates the epithelium from the lamina propria, where the uterine glands, with a simple, tubular morphology, are located. These glands can branch out and increase their tortuosity according to the stage of the cycle (Gray et al., 2001; Hanada, Maeda, & Oikawa, 2012; Van Camp, 1993).

The endometrium is a sterile mucosa that only communicates with the outside during service or delivery. In mares (*Equus ferus caballus*; Linnaeus, 1758), acute post-breeding inflammation of the uterus is a physiological response of the endometrial tissue to the entry of exogenous elements during service. This physiological response is necessary for the effective removal of microorganisms, spermatozoa and other debris in the uterus, as well as extenders, in the case of artificial insemination (Causey, 2006; Troedsson, 1999, 2006). If this acute inflammation persists for more than 48 hours, it becomes a pathological condition (Woodward, 2012). This makes the uterine environment incompatible with the survival of the embryo by the time it reaches

the uterus, around day 6 post-fertilization (Battut, Colchen, Fieni, Tainturier, & Bruyas, 1997).

Persistent post-breeding endometritis is the single most important pathology responsible for subfertility in mares, resulting in large economic losses for the equestrian industry (Troedsson, 1999; Watson, 2000). Furthermore, the specificity and sensitivity of the diagnostic methods could influence its prognosis (Katila, 2016).

Mares can be classified as *susceptible* or *resistant* to post-breeding endometritis according to their response to an experimentally induced infection with *Streptococcus zooepidemicus*. Those females that are able to remove the accumulation of intrauterine fluid within 48 hr are classified as *resistant* to endometritis, and those that do not are classified as *susceptible* to endometritis (Brinsko, Rigby, Varner, & Blanchard, 2003; Fumuso et al., 2007; Hughes & Loy, 1969; Maischberger, Irwin, Carrington, & Duggan, 2008).

Currently, there is no ideal method for diagnosing uterine pathologies in mares (Katila, 2016). However, the widely described endometrial biopsy (Kenney, 1975, 1978; Kenney & Doig, 1986; Leishman, Miller, & Doig, 1982; Ricketts, 1975; Witherspoon, Goldston, & Adsit, 1972) is still the best technique to evaluate the endometrium as it is simple, safe, painless and helpful in the diagnosis and prognosis of reproductive disorders (Ferreira-Dias, Nequin, & King, 1999; Hanada et al., 2012; Katila, 2016; Leishman et al., 1982; Ricketts, 1975). Along with other diagnostic methods, it is used to estimate fertility in accordance with the scale designed by Kenney (1978) and improved by Kenney and Doig (1986). Uterine biopsy is routinely used as it is one of the most sensitive techniques for the diagnosis of alterations by histopathological analysis (Martins, Eigenheer-Moreira, da Leite, & Ferreira, 2011). However, this is still a subjective evaluation (Mansour, Ferreira, Tavares Fernandes, & Henry, 2004).

One way to increase the objectivity is to apply histomorphometry, *that is*, the measurement of histological structures (Mandarim-de-Lacerda, 1994). This technique results in a more objective morphological study that increases the diagnostic accuracy of the endometrial pathologies (Mansour et al., 2004).

Several authors have shown that the height of the endometrial epithelium—both lining and glandular—varies depending on the phase of the oestrous cycle due to the action of hormones. Thus, at oestrus, it is characteristic to observe diffuse hyperplasia and stromal oedema (Brandt, 1970; Kenney, 1978; Kenney & Doig, 1986 Mansour et al., 2004; Van Camp, 1993). Changes are also recorded in response to pathogenic organisms. Therefore, a morphometric study would be a useful addition to the diagnosis (Samuel, Ricketts, Rossdale, Steven, & Thurley, 1979).

The aim of this study was to compare the endometrial histomorphometry of mares either susceptible (SM) or resistant (RM) to persistent post-breeding endometritis in the oestrus phase.

2 | MATERIALS AND METHODS

2.1 | Animals

In this study, 24 Criollo mares, ranging from 3 to 12 years old, weighing from 330 to 500 kg, with known reproductive histories and maintained under the same conditions, were used. These mares were classified as susceptible (SM) and resistant mares (RM), according to the methodology established by Hughes and Loy (1969) with modifications by Fumuso, Aguilar, and Giguère (2006). This methodology allows to classify mares as susceptible or resistant to endometritis based on their ability to remove the intrauterine fluid within 48 hr after experimental inoculation with dead sperm.

2.2 | Approval by the Welfare Committee

The experiment in this study is endorsed by the Animal Welfare Committee of the Faculty of Veterinary Sciences, UNICEN.

2.3 | Samples collection: biopsy and histological processing

For proper collection of the endometrial sample, the manoeuvres were performed after restraining the animal in a gynaecological chute and under conditions of hygiene of the perineal region. The status of the oestrous cycle of the mare was evaluated by ultrasound with a 5-MHz dual, linear transducer (Pie Medical, 360 Vet). The presence of a follicle greater than or equal to 35-mm diameter was considered indicative of oestrus. For sampling, a biopsy forceps designed for horses (54-cm length, 4 mm × 28 mm cut-off area, Jackson Uterine Biopsy Forceps J-116, Jorgensen Laboratories, Inc.) was used.

Samples were taken from the first portion of the uterine horn according to the protocol established by Kenney (1978) and confirmed by Hanada et al. (2012). They were placed in 10% buffered formalin fixative solution for 24 hr. Then, they were stored in 70% ethanol until further histological processing at the Laboratory of Histology of the Department of Biological Sciences of the Faculty of Veterinary Sciences, UNICEN.

From the paraffin-embedded samples, 5-micrometre-thick tissue sections were prepared using a Microm HM 3152 microtome. These histological sections were routinely stained with Haematoxylin-Eosin and placed in an incubator at 30°C for 24 hr for their further mounting with Canada balsam, observation under optical microscope and histomorphometric evaluation.

For the histomorphometric analysis, a binocular optical microscope (MOTIC® Microscope) with a micrometre eyepiece was used. The general histoarchitecture of each sample was observed, and the height of the lining and glandular epithelia (LE and GE, respectively), the diameter of the endometrial glands and the number of endometrial glands per field were determined. For the assessment of the epithelial heights and the glandular diameters, 12 endometrial biopsies (6 SM and 6 RM) were evaluated, and to determine the glandular density, 24 endometrial biopsies (13 SM and 11 RM) were used.

For the determination of the height of the epithelia, the distance from the basement membrane to the apical edge of the epithelial cell was measured (Mansour et al., 2004), with a magnification of 100×. For each of the individual samples, each one of the assessments was performed as follows: (i) for the epithelial height, 30 measurements of each epithelium type (lining and glandular) were made and expressed

in micrometres (Figures 1 and 2); (ii) for glandular diameter, the means were estimated by measuring two diameters at right angles in 30 circular section glands randomly selected, examining the entire slice surface, in both the spongiosum and compactum strata, and were expressed in micrometres (Figure 3); (iii) for glandular density, the glands present in 10 fields were counted in the spongiosum and compactum strata using a 40× magnification, and were expressed as glands per field (Figure 4).

2.4 | Statistical analysis

The data obtained were statistically analysed by Student's *t* test using the GraphPad InStat software (GraphPad Software Inc., CA, USA). Data are presented as mean ± standard deviation.

3 | RESULTS

In accordance with the previous description, the analysed endometrium, in both resistant and susceptible mares, was integrated by simple columnar lining epithelium and loose connective tissue stroma. The epithelial cells presented acidophilic cytoplasm, with elongated densely stained nuclei, predominantly located in the basal third of the cell. The stroma consisted of loose connective tissue with fibroblasts and collagen fibres. In this layer, oedema, some inflammatory cells and endometrial glands were observed dispersed at both the stratum compactum and spongiosum. Those glands presented simple cuboidal glandular epithelium, with acidophilic cytoplasm with secretory granules, and round densely stained nuclei.

For the height of the lining and glandular epithelia, significant differences were not observed within each group of mares. When comparing the data between the two groups, significant differences ($p < .05$) were observed for all of the variables (Table 1). Thus, epithelial height and glandular diameter were both greater in susceptible

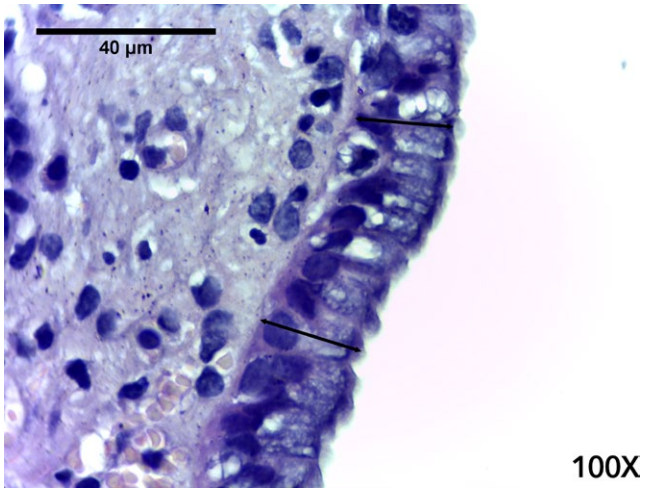

FIGURE 1 Microphotography at 100× exemplifying the measurement of endometrial lining epithelium height; the height was measured as the distance from basal lamina to apical border

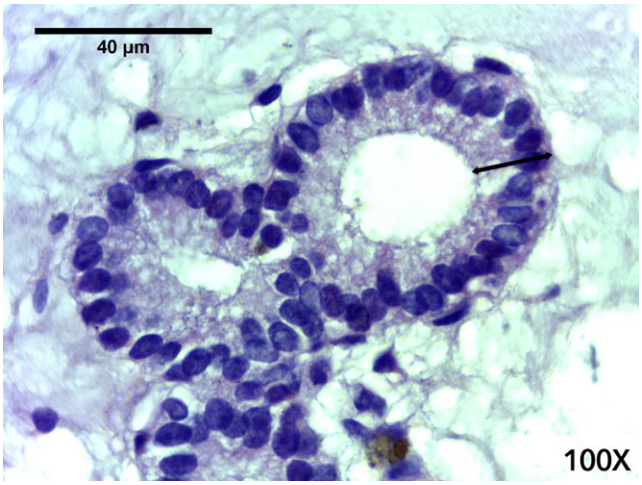

FIGURE 2 Measurement of glandular epithelium at 100×, the same criterion used for lining epithelium was applied

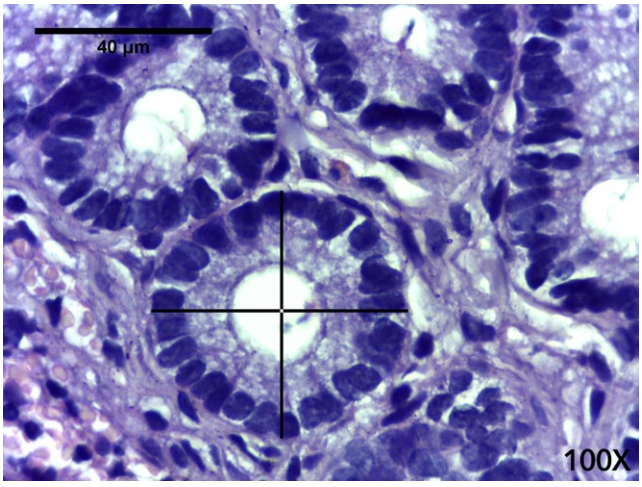

FIGURE 3 Measurement of glandular diameters at 100×; for each sample, two perpendicular measures were registered

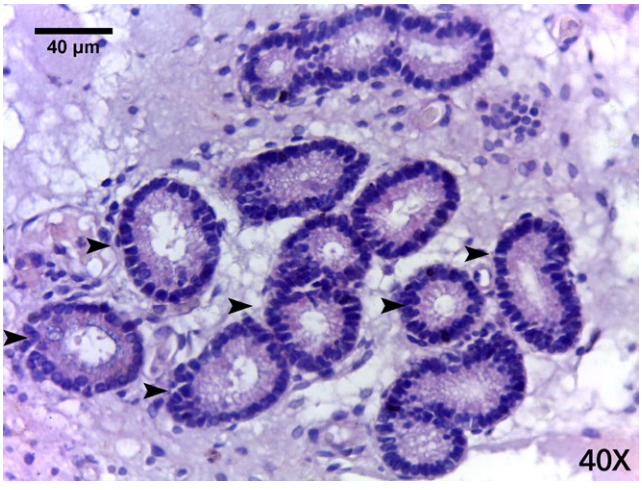

FIGURE 4 Microphotography at 40× magnification showing uterine glands as performed to calculate glandular density per field; arrowheads mark out some glands as an example

TABLE 1 Height of the lining and glandular epithelia, glandular diameter and glandular density of mares resistant (RM) and susceptible (SM) to post-breeding endometritis

	Height of lining epithelium	Height of glandular epithelium	Glandular diameter	Glandular density
	µm (Mean ± SD)			Glands/field (Mean ± SD)
RM	13.3 ± 4.1[a]	13.0 ± 2.6[a]	44.8 ± 8.6[c]	20.5 ± 3.3[e]
SM	15.9 ± 6.9[b]	15.0 ± 5.2[b]	51.3 ± 17.0[d]	24.8 ± 6.1[f]

Different superscripts indicate statistically significant differences within each column [a,b]$p < .01$; [c–f]$p < .05$.

mares, with a glandular density which was also greater than that found within resistant mares.

4 | DISCUSSION

The epithelium and the stroma of the healthy endometrium show cyclic morphological variations as a result of hormonal changes (Lehmann et al., 2011). It is important to know the patterns of proliferation and the histological changes during the oestrous cycle to be able to study the alterations that might occur (Mansour, Moreira, & Ferreira, 2015). Furthermore, the integrity of the endometrial epithelium plays an important role in the resistance to infections (Causey et al., 2010).

The histological examination of an endometrial biopsy is the most reliable diagnostic test for endometritis and uterine infections (Nielsen, 2005). By means of this test, it is possible to detect inflammatory responses to infectious agents and to evaluate chronic, degenerative endometrial disorders, all by the same procedure (Leishman et al., 1982; Ricketts, 1999).

No references were found regarding either the existence of post-coital endometritis in other species or a comparable classification of resistance to endometritis as the one used in mares. Nevertheless, some studies exist about the relationship among the endometrial histomorphology and infertility in females.

In women, endometrial hyperplasia (Sharma, Saxena, & Khari, 2016) and lower gland density with greater glandular epithelium (Li et al., 1993) were reported as causes of infertility. In rats with exogenous gonadotrophin stimulation, Kramer, Stein, and Van der Walt (1990) observed that early increased in lining and glandular epithelia heights, among others changes, affect implantation, and hypothesized that the same may occur in women under in vitro fertilization programs.

Hsueh, Erickson, and Lu (1979) reported that aged rats presented higher epithelium, among other changes, and related those with lower reproductive performance. However, Tchokonte-Nana and Longo-Mbenza (2011) observed that in rats treated with peanut oil, higher epithelia were associated with higher fertility and pup delivery.

In cows, Cupps (1973) identified histomorphological changes in sterile animals. In endometritic cows, Rhyaf (2010) and Dolatkhah et al. (2013) observed luminal epithelial hyperplasia and glands atrophy with a greater dispersal. However, no epithelial and glandular alterations were reported by Singh, Singla, Dhaliwal, Kumar, and Banga (2008) in repeated breeding cows. Furthermore, in camels with endometritis, uteri presented hyperplasic epithelium with increased cytoplasmic inclusions and vacuoles (Fetaih, Pospischil, & Waldvogel, 1992).

Mansour et al. (2004) performed a histomorphometric analysis in mares, which were grouped according to the categories described by Kenney and Doig (1986). These authors compared oestrus vs. di-oestrus data and they observed higher epithelial height in mares of category IIa (Kenney & Doig, 1986), in both phases. However, they did not find significant differences between the heights of the epithelia in the same phase of the cycle, even when the height of LE was greater than that of the GE, probably due to a lower activity of the glands in deeper strata. They considered that the histomorphometric study of the glandular lumen would be useful to recognize glandular atrophy or cystic glands, which is of great value in the prognosis of endometrial conditions.

Leishman et al. (1982) studied normal mares and mares with a history of infertility, based on the condition of endometriosis. These authors did not observe significant differences in the height of LE between groups. Furthermore, they did not find differences in the density of the glands, except for the chronically infertile group, which presented a lower glandular density.

Leishman et al. (1982) and Mansour et al. (2004) found variability in the glandular density within groups. The authors attributed this to changes in the oestrous cycle, as well as to individual variations in the glandular density.

Despite having used a similar methodology, it is not possible to trace an analogy with the present study as the population assessed is different in terms of its reproductive conditions. The results of our study suggest the existence of a relationship between the evaluated endometrial histomorphometric characteristics and the susceptibility to persistent post-breeding endometritis in mares. This would indicate that the higher susceptibility to endometritis would be related to increased epithelial height, greater glandular density and greater glandular development during oestrus. Future studies could address the modifications through other phases of the oestrous cycle, if any, regarding the cellular organization in epithelium and stroma, in addition to how it may vary in accordance with resistance to endometritis and what may be the factors that provoke such variations.

It is important to emphasize the significance of the histological analysis—both morphometric and pathological—of the endometrium in mares of breeding programs, which would mean an improvement in

the diagnosis of females with reproductive disorders and a reduction in economic losses.

CONFLICT OF INTEREST

The authors have no conflict of interest regarding the content of this manuscript.

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How to cite this article: Herrera M, Herrera JM, Cantatore S, Aguilar J, Felipe A, Fumuso E. Comparative histomorphological study of endometrium in mares. *Anat Histol Embryol*. 2018;00:1–6. https://doi.org/10.1111/ahe.12335