Review

Is adenomyosis a problem in reproduction and fertility?

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Abstract

Adenomyosis is defined as the presence of glandular foci beside the endometrium of uterus: in the myometrium and/or perimetrium depending on the progress of the disorder. So far, adenomyosis has been diagnosed in women and rodents, and studies conducted on cows have been rare. In this review we: (1) summarize the knowledge regarding adenomyosis, (2) compare the symptoms and aetiopathology between women and cows, (3) describe angiogenic uterine processes related to adenomyosis development and (4) outline the influence of adenomyosis on proper fertility processes in cattle (conception and fertility rates).

Key words: adenomyosis, uterus, cow

Adenogenesis in uterus

During the estrous cycle, endometrial tissue undergoes structural and functional changes that enable the establishment of gestation. Steroid hormones, in particular estrogens, regulate numerous uterine processes, in which adenogenesis comprises epithelial cell proliferation and gland development. Unexplained peri-implantation embryonic loss in humans and livestock may reflect unrecognized defects in endometrial adenogenesis. Abnormalities in adenogenesis potentially lead to uterine disease, such as adenomyosis, defined as the presence of endometrial glands with stromal elements in the myometrium layer of the uterus. It is important to distinguish the aetiological factors in women, where adenomyosis is already diagnosed, and female animals, because differences exist in the morphology of the uterus. In cows, the endometrium consists of aglandular caruncles, stromal protuberances and glandular intercaruncular areas (Gray et al. 2001). In women, the junctional zone lies between the endometrial mucosa and the inner myometrium which undergoes cyclical changes and is the component of the endometrial-myometrial barrier with peristaltic activity (Ferenczy 1998).

Adenomyosis progression and subtypes

The uterus, both the endometrium and myometrium, undergoes many morphological and physiological changes throughout the estrous cycle in response to progesterone and estrogen (Fig. 1). These hor-

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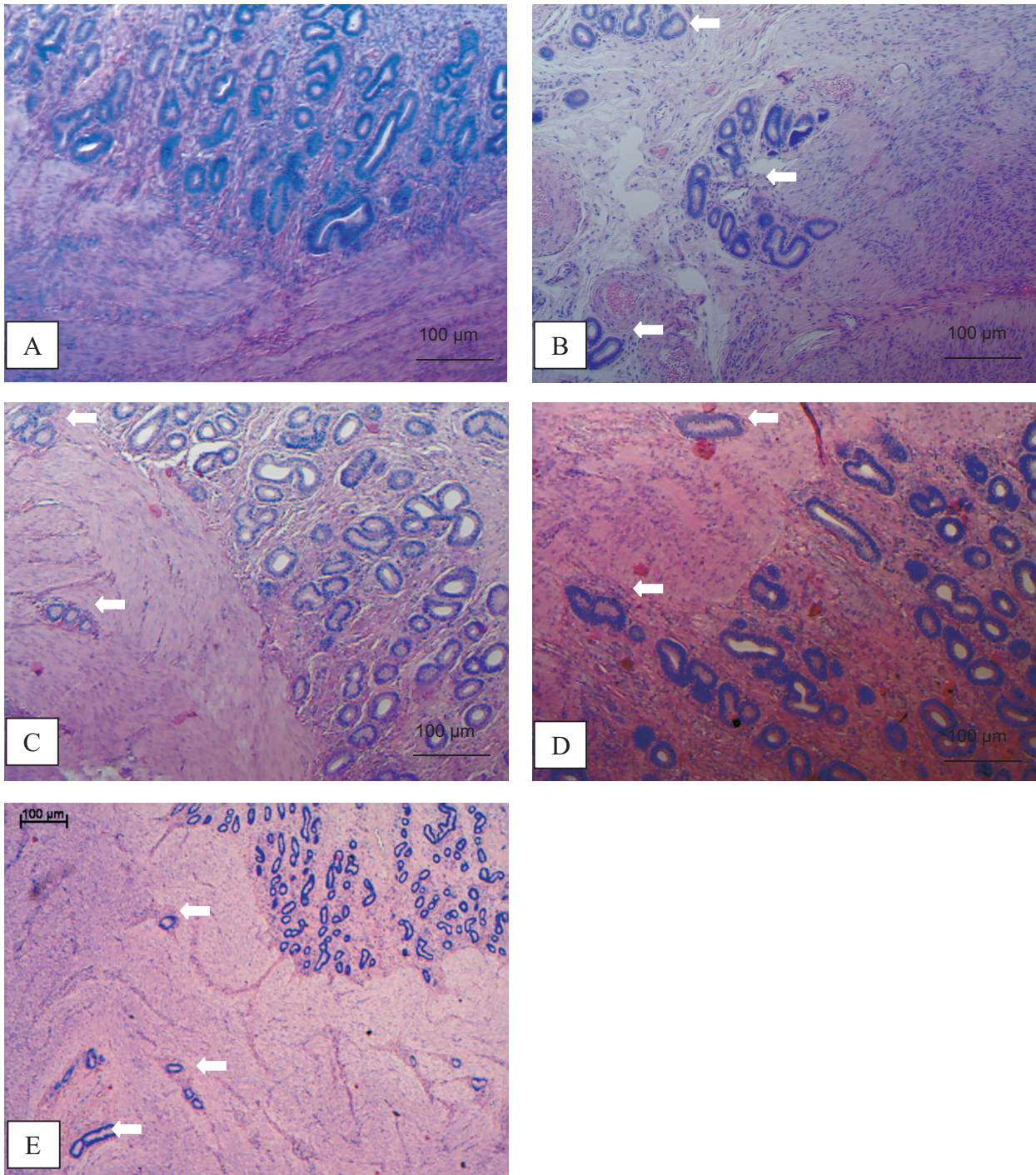
Fig. 1. Representative images of haematoxylin/eosin-stained bovine uteri: healthy (A) and adenomyotic (B-E). Arrows indicate glands beside the stroma layer, placed in the myometrium or near blood vessels in the myometrium of uteri characteristic for adenomyosis. (Magnifications: A-D x 200, E x 100).

mones influence endometrial cell function by inducing the synthesis and secretion of other signaling molecules or modulating the presence of receptors for these agents (Shemesh et al. 2001). Proper remodeling of vascular and non-vascular tissues in the endometrium and the endocrine aspects related to cell function and dynamic changes during the estrous cycle determines successful insemination and pregnancy. Adenomyosis may disturb the functionality of the uterus.

The extent of adenomyosis in uterine tissue obtained by hysterectomy is assessed by determining the distance from the deepest glandular nest to the lower border of the endometrium (Azziz 1989). In cattle,

adenomyotic changes in uterine tissues are divided into four stages according to the depth of endometrial foci in the myometrium after microscopic observation of hematoxilin/eosin-stained samples (Katkiewicz et al. 2005). In the first stage (I), nests are present within the perivascular connective tissue, slightly crossing the mucosal-myometrial border. The second stage (II), is characterized by the presence of glandular nests in the inner layer of uterine smooth muscle, in the third stage (III), foci penetrate deeper into the outer myometrium layer, and in the fourth stage (IV), nests are present within the serosa (Katkiewicz et al. 2005). We compared the various locations for collecting uterine samples: ipsilateral to the active ovary, near the cervix and the middle segment of the uterus contralateral to the active ovary (days 8-12 of the estrous cycle). The results demonstrated that the frequency of adenomyosis did not change based on the sampling location in the uterus (Korzekwa et al. 2013). Moreover, in cows, there is a strong correlation between the frequency and progression of adenomyosis and age. Cows older than 5 years have a higher rate of adenomyosis subtype IV, which is potentially a more advanced stage of this disorder (Korzekwa et al. 2013).

The influence of adenomyosis on fertility

Adenomyosis is usually diagnosed by histopathological examination of the uterus after a hysterectomy, and it is difficult to determine whether this disease directly impairs fertility. Adenomyosis preferentially affects multiparous women in their reproductive and premenopausal years; however, several studies have shown that this disorder is also present in young, nulliparous women (Campo et al. 2012). Recent studies have shown that women with adenomyosis exhibit decreased HOXA10 gene expression in the endometrium. HOXA10 is important for successful embryo implantation and its decreased expression may cause implantation defects in women (Fisher et al. 2011).

The influence of adenomyosis on fertility is not elucidative in animals and there are few studies so far (Katkiewicz et al. 2005, Moreira et al. 2011, Korzekwa et al. 2013). Thus the consequences for insemination, implantation and pregnancy development are not yet confirmed, and it is still unclear if adenomyosis is a positive, neutral or negative process. This review indicates that adenomyosis also occurs in cows, especially in older animals, and potentially modifies the reproductive processes during the estrous cycle.

Physiological and pathological angiogenesis in the uterus

Throughout reproductive life, the endometrium undergoes dynamic changes which range from cellular proliferation and differentiation to tissue breakdown and renewal. Because of its particular physiology, the endometrium is among the few adult tissues that are capable of self-renewal. Angiogenesis plays a pivotal role in the remodeling of endometrial tissues. Angiogenesis in the endometrium has unique characteristics, which are not present in other tissues (Masuda et al. 2010).

The endometrium is the mucosal lining of the uterus, and the *zona functionalis* is the part of the endometrium that undergoes regeneration, differentiation and disruption during each cycle. The blood supply for this functional layer arises from the arteries in the basal endometrium (*zona basalis*). The arteries in the basal endometrium originate from the arcuate arteries that cross the myometrium, the external muscular layer of the uterus. The smooth muscle that coats the blood vessels gradually disappears in the progression towards the functional layer of the endometrium. As a result, the vessels of the *zona functionalis* consist only of endothelial cells. The arterioles in the *zona functionalis* undergo progressive spiralisation and permeabilisation towards the secretory phase of the cycle (Iruela-Arispe et al. 1999, Masuda et al. 2010).

Estrogen is a proliferative stimulus before ovulation, during the proliferative phase of the cycle. In this phase, a new layer of *zona functionalis* grows rapidly, supported by the concomitant formation of new capillaries. In humans, endothelial cells are highly mitogenic during the proliferative phase, whereas in ruminants such as the cow, the greatest vascularization is encountered during the luteal phase. After ovulation, progesterone (P4) levels rise, resulting in the differentiation of endometrial tissue and vascular remodeling. In this phase of the cycle, angiogenesis is suppressed and cellular differentiation is promoted (Iruela-Arispe et al. 1999).

Unlike in non-reproductive organs, the endothelial cells that reside in the endometrium are highly sensitive to steroid hormones. Uterine arteries, but not the arterial walls of non-reproductive tissues, express receptors for estrogen and P4 (Iruela-Arispe et al. 1999). This allows estrogen and P4 to act directly on the uterine vasculature. Nevertheless, the activity of steroid hormones in the uterus is primarily mediated by the uterine microenvironment. Stromal and immune cells present in the uterine milieu regulate angiogenesis and vascular remodeling (Kuroda et al. 2013). Many pro-angiogenic and anti-angiogenic

modulators are expressed in the endometrium (Becker et al. 2006, Sağsöz and Saruhan 2011). Their expression varies during the cycle, and these factors often exhibit heterogeneous localization. Among the pro-angiogenic stimuli are vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), metalloproteinases (MMPs), cytokines and angiopoetins. There are several mechanisms which restrict angiogenesis in the female reproductive tract. For example, thrombospondin 1, endostatins and transforming growth factor (TGF) β suppress the proliferation and the migration of endothelial cells (Edwards et al. 2011).

Because angiogenesis rarely occurs in adult tissues, it requires strict regulation to avoid the onset of pathologies, such as abnormal uterine bleeding, uterine fibroids, adenomyosis, endometriosis and carcinomas. In women, steroid hormones and P4 in particular, play a role in this specific dysfunction (Hickey et al. 1999), while in cows such processes are not so far the subject of studies.

Uterine fibroids are often associated with dysfunctional menstrual bleeding. These tumors reveal an altered expression pattern of angiogenic modulators, including VEGF and MMPs (Di Tommaso et al. 2013). In humans, adenomyosis causes dramatic alterations in the expression pattern of angiogenic modulators (Kang et al. 2010). There is considerable evidence for the close relationship between adenomyosis and angiogenesis.

Similarities and differences between adenomyosis and other uterine dysfunctions

Adenomyosis and endometriosis, with the exception of ovarian endometriomas, used to be considered as one disease: "adenomyoma". As such, the early history of adenomyosis is interwoven with that of endometriosis until the mid-1920s, when the two conditions were finally separated (Brosens et al. 2012). Endometriosis is diagnosed as an age-independent fertility disturbance disorder, whereas in adenomyosis, disease progression correlates with age and the influence on fertility remains under investigation (Campo et al. 2012, Korzekwa et al. 2013). Ectopic endometriotic nests are located in the outer epithelium of the uterus, other reproductive organs, and in the gastrointestinal tract (Benagiano and Brosens 2012). Adenomyosis and endometriosis may represent different phenotypes of a more profound disorder characterized by impaired cellular responses to ovarian sex steroids throughout the reproductive tract (Leyendecker et al. 2009, Benagiano and Brosens 2012).

Another process of morphological and functional dysfunction of uterus is endometrosis. The use of the term endometrosis in mares was introduced by Kenney (1992). It is defined as active or inactive periglandular and/or stromal endometrial fibrosis including glandular alterations within fibrotic foci (Kenney 1992). In mares, the severity of endometrosis increases with age, which is also a characteristic of adenomyosis, but there is no association with the number of foalings (Kenney 1992). The morphological/immunohistochemical characteristics correspond to different developmental stages of endometrosis, which are independent of uterine regulatory mechanisms. Although neither seasonal nor cyclical endocrine changes seem to influence the progression of this disease, inflammation, such as endometritis, appears to substantially activate the process; future studies are required for clarification (Hoffmann et al. 2009). Until now, little has been known concerning the aetiology and pathogenesis of this major cause of equine infertility (Hoffmann 2009). Nevertheless, the aetipatology for the above processes may be similar.

Aetiology of adenomyosis

Trauma – dependent cause of adenomyosis

One possible mechanism of adenomyosis development involves the breakdown of the endometrium-myometrium barrier which results from trauma and the subsequent reactive hyperplasia of the basal endometrium and penetration into the myometrial layer (Azziz 1989, Levgur et al. 2000). Interventions in women, such as laparoscopic myomectomy or pregnancy termination potentially lead to the development of adenomyosis (Levgur et al. 2000). Animal models support the concept of trauma as a cause of adenomyosis. In rabbits, removing the products of conception from one uterine horn by curettage and enabling pregnancy to develop properly in the contralateral horn resulted in adenomyosis of the emptied horn (Levgur et al. 2000). Leyendecker et al. (2009) hypothesized that adenomyosis may arise spontaneously from chronic peristaltic activity of the uterus or hyperperistalsis. This may cause microtrauma to the uterine tissues, inducing "tissue injury and repair" (TIAR) mechanisms. The activation of TIAR mechanisms results in the local production of estrogens, and may cause infiltration of the basal endometrium deep into the myometrial wall (Leyendecker et al. 2009). Endometriotic cells have invasive potential and are capable of migrating by amoeboid contraction and expansion, which enables endometrial cells to penetrate into the myometrium after the en-

dometrium-myometrium border breaks down (Ferenczy 1998, Li et al. 2012).

It is possible that, in cows, gynecological interventions and other circumstances such us endometritis may lead to mucosal-myometrial barrier break down and as a result these conditions may be the cause of adenomyosis development in the uterus.

Metaplasia process

The theory of adenomyosis aethiology involves the spontaneous transformation of stem cells into endometrial cells in response to exogenous stimuli. In 2004, for the first time, stem cells were identified in the adult human endometrium (Chan et al. 2004). These cells exhibited clonogenic activity, indicating that stem/progenitor cells may play a pivotal role in endometrium renewal (Chan et al. 2004, Masuda et al. 2010). Xu et al. (2011) identified stem cells in the murine endometrium, and showed that estradiol (E2) promoted their proliferation and differentiation *in vitro*, further supporting the hypothesis that stem cells are involved in mammalian endometrial regeneration. Endometrial stem cells are multipotent and are able to differentiate under proper conditions into numerous cell types, for example epithelial or stromal cells (Gargett 2006). There is less evidence for existence of stem cells in the myometrium but some studies indicate that a population of myometrial cells behaves like stem cells (Maruyama et al. 2010). The presence of stem/progenitor cells in the uterus provides evidence that these cells are involved in the aetiology of adenomyosis. Glandular nests may arise *de-novo* deep in the myometrium from undifferentiated stem cells in response to exogenous stimuli. Mesenchymal stem cells may also migrate to uterine tissues from the bone marrow with blood or through the lymphatic vessels, and once there they may differentiate into endometrial epithelial cells under E2 influence (Gargett 2006, Zhang et al. 2012). Our recent studies on bovine uterine cells also suggest the involvement of stem cells in the pathogenesis of adenomyosis. We identified pluripotent markers (Sox2, Oct3/4 and Nanog) in uterine cells by flow cytometry assay and in bovine uterine tissues, in the endometrium as well as in the myometrium, by immunohistochemical staining.

Immunological abnormalities and inflammation

The endometrial environment in adenomyosis differs from that in healthy females (Ota et al. 1998). Endometrial cells and leukocytes produce cytokines in response to steroid hormones, which influence reproductive processes. Interleukin (IL)-8, produced by endometrial cells and monocytes, stimulates endometrial cell proliferation and angiogenesis, which may be important for glandular nest formation (Arici et al. 1998). Epithelial cells in adenomyotic foci express significantly higher levels of IL-8 and monocyte chemotactic protein-1 (MCP-1) compared with normal endometrial cells (Ulukus et al. 2005). Another cytokine which may play an important role in the pathophysiology of adenomyosis is IL-10. Wang et al. (2009) demonstrated that this cytokine was abundantly produced by ectopic and eutopic endometrial epithelial cells from the tissues of women with adenomyosis. According to Tremellen and Russell (2012), there was a higher density of macrophages and natural killer cells in the stroma of women with adenomyosis when compared with that of healthy women. An *in vitro* study by Yang et al. (2006) revealed that macrophages increased mRNA expression of interleukin-6 in coculture with endometrial stromal cells from the eutopic endometrial tissue of women with adenomyosis. Eyster et al. (2010) used DNA microarrays to demonstrate that macrophage-secreted factors downregulated expression of integrin alpha-6 and upregulated IL-8/chemokine ligand 8, phospholamban, nicotinamide N-methyltransferase, matrix metalloproteinase 3, connective tissue growth factor, tenascin C and cysteine-rich angiogenic inducer 61. These results indicated that reciprocal communication exists between macrophages and endometrial stromal cells, and point to another immunological mechanism which may be involved in the formation of ectopic implants and pathogenic angiogenesis during the pathogenesis of adenomyosis (Eyster et al. 2010).

Hormonal dependency

The dysregulation of cyclicity and pathological hormonal stimuli are likely causes of uterine lesions (Katkiewicz et al. 2005). In women and cows with endometriosis and adenomyosis, the uterine tissue is P4 resistant because of reduced or inhibited signaling through P4 receptors (Aghajanova et al. 2011, Korzekwa et al. 2013). As a consequence of P4 resistance, the expression of several key steroidogenic genes is not induced during implantation, leading to implantation failure and infertility (Dusza et al. 2006, Aghajanova et al. 2011, Al-Sabbagh et al. 2012, Korzekwa et al. 2013). Similar to endogenous E2, phytoestrogens bind both E2 receptors (α and β) and mimic, modulate, or inhibit the endocrine system through these interactions (Dusza et al. 2006), which is especially important in ruminants fed phytoestrogen-rich feed. Because E2 signaling promotes prolif-

eration, the ability of E2 receptors to bind many ligands, including phytoestrogens and other endocrine disruptors, is a concern (Dusza et al. 2006). In addition, the modification of P4 and E2 activity might promote changes in adenomyotic tissue, such as HOXA11 (Szczepańska et al. 2012), chemokines (Li et al. 2012), cytokines (Ulukus et al. 2005) and lipoxins (Szczepańska et al. 2012). In cows, the aspect of P4 resistance is considered in the postpartum period during bacterial infection (Lewis 2003). Endometrial gland morphology in cows is associated with circulating P4 concentrations during the early luteal phase as showed by Wang et al. (2007). This suggests that P4 resistance observed during adenomyosis may reflect not the permanent pathological status of the uterus, but the status maintaining throughout only one estrous cycle, when P4 production was modified. Disturbances in the E2-P4 equilibrium, related to changes in secretion and activity in the reproductive tract, play a fundamental role in the development of adenomyosis (Ferenczy 1998, Korzekwa et al. 2013). Adenomyosis was observed in 44% of all examined cows and the frequency and progression increased with age. Aromatase staining and its protein expression were stronger in adenomyotic cows and increased with disease progression. Progesterone receptor (isoforms A and B) immunoreactivity was observed in all adenomyotic foci and adjacent healthy endometria in the cytoplasm of the epithelial layer surrounding the glands of both the eutopic endometrium and the adenomyotic foci. Stronger and more diffuse cytoplasmic E2 receptor immunoreactivity was detected in the endometrium and the myometrium of adenomyotic foci compared with the normal endometrium. Higher concentrations of E2 but not P4 were noticeable also in the serum of adenomyotic cows compared with those from healthy cows (Korzekwa et al. 2013).

The immunoexpression of the proliferative factor Ki67 was increased in adenomyotic cows (Katkiewicz et al. 2005). Studies conducted in women demonstrated that adenomyosis disturbs reproductive health because adenomyotic foci potentially develop into carcinomas (Ferenczy 1998).

Another important factor that may regulate adenomyosis pathogenesis is prostaglandin E2 (PGE2). PGE2 is produced by macrophages and ectopic endometrial cells and increases estrogen synthesis. It stimulates the proliferation of endometrial cells, suppresses immune reactions and is anti-apoptotic and angiogenic. These actions contribute to the pathogenesis of endometriosis and may also play a role in adenomyosis development (Wu et al. 2010).

Diagnosis and treatment

The principal way to diagnose adenomyosis is by histology of hysterectomy specimens, which excludes further gestation (Ferenczy 1998). In women, there are a few non-invasive methods to diagnose adenomyosis such as: transabdominal and transvaginal sonography and MRI (magnetic resonance imaging), which appears to be more specific and sensitive for diagnosing adenomyosis compared with ultrasonographic examination (Levy et al. 2013).

The pharmacological treatment of adenomyosis in women focuses on inhibiting the action of the estrogens, thereby relieving the symptoms. Treatment options include the following: inhibiting local aromatase production with selective estrogen receptor modulators, estrogen-progestin combinations, and gonadotropin-releasing hormone agonists (Benagiano and Brosens 2012). Another potential target for adenomyosis treatment is the abnormal immune response by immunomodulators and anti-immflamatory agents (Kappou et al. 2010). A popular treatment for adenomyosis and endometriosis in women is dienogest, synthetic progestin. It suppresses ovarian estrogen biosynthesis and targets the expression of genes involved in prostaglandin synthesis (Benagiano and Brosens 2012).

Until now, adenomyosis in cows has not been diagnosed routinely by veterinarians. Endometrial biopsy allows for the diagnosis of degenerative processes and changes in chronic inflammation (Bonnett et al. 1991) and would potentially be useful also for adenomyosis diagnosis in cows. Biopsies were initially performed in mares in the 1960s as a tool to investigate infertility. This method takes into consideration inflammation and fibrosis of the endometrium and then provides an estimation of a mare's ability to conceive and maintain a pregnancy to term. Over the years, endometrial biopsy has proven to have both diagnostic and prognostic value in evaluating the fertility of a mare (Kenney 1992). In cattle, biopsies are less popular because they are more difficult to perform. Bovine reproduction researchers have been reluctant to perform endometrial biopsies because it has been suggested that this procedure can impair subsequent fertility by inducing uterine pathology (Zaayer and van der Horst 1986). Nevertheless, the technique has the potential to play a key role in assessing endometrial health and investigating physiological or disease processes. It is possible to perform an endometrial biopsy during any stage of the oestrous cycle in cows but it is the easiest to perform during oestrus when the cervix is relaxed. According to Chapwanya et al. (2010), after cleaning the perineum and external genitalia, the biopsy instru-

ment is introduced in a protective sheath into the vagina and guided through the cervix by manipulating per rectum. Nowadays, the endometrial biopsy described by Chapwanya has became more common and has significant diagnostic utility in bovine reproduction.

Nevertheless, diagnosis of adenomyosis in cows for monitoring the reproductive status in breeding is debatable because the relevance of adenomyosis in women and cows is different. In women, the accurate diagnosis of adenomyosis is mainly required for differentiation of this condition from other diseases including cancer. Histological diagnosis requires full thickness uterine biopsies, commonly obtained after hysterectomy in women. Alternative non-invasive diagnostic methods (e.g. magnetic resonance imaging, sonography) are promising in human medicine but they are not practical in dairy herds. More studies are needed to show the impact of adenomyosis on fertility parameters in cows.

Summary

In this review we: (1) summarized the knowledge regarding adenomyosis, (2) compared aetiopathology between women and cows, (3) described angiogenic uterine processes that are related to adenomyosis development and (4) outlined the influence of adenomyosis on fertility processes.

The genesis of adenomyosis remains debatable. Although studies of adenomyosis as morphological and functional dysfunction of the uterus are supplemented by the latest papers, the molecular mechanism governing aetiology and changes in P4/E2 equilibrium still remains unknown (Aghajanova et al. 2011, Korzekwa et al. 2013). Adenomyosis diagnoses are rare, but in the future angiogenic or anti-angiogenic, and anti-inflammatory factors or the identification of compounds affecting stem cell differentiation, may prove to be effective therapeutic agents and markers in clinical recognition of this dysfunction also in cattle breeding.

Acknowledgments

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