

Equine post-breeding endometritis: A review

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The deposition of semen, bacteria and debris in the uterus of the mare after breeding normally induces a self-limiting endometritis. The resultant fluid and inflammatory products are cleared by 48 hours post cover. Mares that are susceptible to persistent post-breeding endometritis (PPBEM) have impaired uterine defence and clearance mechanisms, making them unable to resolve this inflammation within the normal time. This persists beyond 48 hours post-breeding and causes persistent fluid accumulation within the uterus. Mares with PPBEM have an increased rate of embryonic loss and a lower overall pregnancy rate than those without the condition. To enhance conception rates, mares at high risk need optimal breeding management as well as early diagnosis, followed by the most appropriate treatment. This article reviews the pathogenesis, diagnosis and treatment of PPBEM and the management of affected mares.

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Introduction

Persistent post-breeding endometritis (PPBEM) is the third most common medical condition of adult female horses (Traub-Dargatz *et al.*, 1991) and the major reason for failure to conceive (Gutjahr *et al.*, 2000). It affects approximately 15% of Thoroughbred mares after natural cover (Zent *et al.*, 1998). Due to its association with decreased fertility, it is of major concern to breeders and veterinary practitioners (Watson, 2000).

Early embryonic death rates are three times higher in mares with this condition than in normal mares (Malschitzky *et al.*, 2003), making it an important cause of loss to the bloodstock industry.

The aim of this article is to review the pathogenesis, diagnosis and treatment of PPBEM and the management of affected mares. It aims to provide breeders with a better understanding of the disease and enable them to optimise their breeding management in order to reduce its incidence. It also aims to update practitioners, allowing them to detect such mares early and administer the most appropriate and successful treatment.

Pathophysiology of PPBEM

Inflammation of the endometrium is caused by a response to exogenous materials introduced directly into the uterus at breeding (Troedsson *et al.*, 2001). These include components

of the semen, extender (in the case of AI), bacteria and other debris (Troedsson, 1999; Troedsson *et al.*, 2001; Causey, 2006).

The normal endometrial inflammatory response, which is triggered by these antigens, is a predictable, physiological event (Troedsson *et al.*, 2001). It is most commonly seen within a half to one hour of breeding (Katila, 1996) and is necessary to clear dead spermatozoa and bacteria from the uterine lumen (Troedsson, 1999).

The influx of polymorphonuclear neutrophils (PMNs) into the uterine lumen and their phagocytic activity after opsonisation of the target (Katila, 1996; Troedsson, 1999; Troedsson *et al.*, 2001) is followed by myometrial contractions regulated by prostaglandin F₂α and oxytocin (Troedsson, 1999). This uterine defence mechanism peaks at around six to 12 hours post insemination (Katila, 1996). In the normal mare, most of the inflammatory products are cleared by physical uterine clearance mechanisms within 48 hours of cover (Katila, 1996). Because the embryo leaves the uterine tube and enters the uterus on about days five to six post-ovulation (Betteridge *et al.*, 1982), the uterine inflammation has to be under control by 96 hours post-ovulation to maximise survival of the embryo (Troedsson, 1999). A mare that is susceptible to PPBEM is unable to clear such fluid by 96 hours and the resulting prolonged inflammation generates an embryo-toxic environment



Figure 1a: A healthy vulva. The labiae of the vulva are symmetrical and the vulva itself is properly closed.

(Troedsson, 1999; Troedsson *et al.*, 2001).

In addition to this, premature lysis of the corpus luteum is caused by complement products. Leukotriene B₄, prostaglandin E and prostaglandin F₂α (Rambags *et al.*, 2003), and subsequent progesterone deficiency, all contribute to embryo mortality (Rambags *et al.*, 2003). Prolonged inflammation may be caused by several factors. Post-ovulatory artificial insemination (AI) more than 12 hours post-ovulation may influence the predisposition towards PPBEM, as rising progesterone levels may decrease uterine defence and uterine clearance (Katila, 1996; Watson *et al.*, 2001). In contrast, AI undertaken between 12 hours pre-ovulation and four to eight hours post-ovulation has no influence on fluid accumulation or pregnancy rate (Watson *et al.*, 2001). Two artificial inseminations within 24 hours during oestrus (in the absence of seminal plasma) profoundly reduce fertility, since the second insemination takes place when the uterine inflammation is at its peak (Alghamdi *et al.*, 2004). Although spermatozoa can survive in a uterine environment already inflamed by an initial insemination, their motility is progressively reduced due to their aggregation with PMNs (Alghamdi *et al.*, 2001). This results in a reduction in the number of viable spermatozoa reaching the uterine tube for fertilisation (Alghamdi *et al.*, 2004; Troedsson *et al.*, 2005).

The use of spermatozoa with reduced seminal plasma (as in frozen/thawed semen or sperm 'packed' from fresh semen by centrifugation) results in a more marked and prolonged inflammatory response (Troedsson *et al.*, 2001),

because seminal plasma is a modulator of sperm-induced inflammation (Troedsson, 1999; Troedsson *et al.*, 2001) and protects viable spermatozoa from opsonisation and phagocytosis (Troedsson *et al.*, 2001).

It is commonly assumed that mares that are susceptible to PPBEM are older maiden (LeBlanc *et al.*, 1998; Pycock, 2006) or multi-parous mares (LeBlanc *et al.*, 1998; Cadario *et al.*, 1999a, 1999b; Hurtgen, 2006) with a history of repeated fluid accumulation (Pycock, 2006) and low fertility rates (Zent *et al.*, 1998). However, new studies by Veronesi *et al.* (2006) show that the average age of normal mares (14 years) and susceptible mares (16 years) is not significantly different. Rigby *et al.* (2001) also suggest that myometrial dysfunction in mares with PPBEM is not dependent on age or pregnancy number.

Delayed uterine clearance of bacteria, fluid and debris following mating (Nikolakopoulos and Watson, 2000) may be caused by many different factors. These include: decreases in the frequency, intensity and duration of the myometrial activity (Nikolakopoulos and Watson, 1997; Troedsson, 1999; Rigby *et al.*, 2001); vascular changes in the endometrium (Troedsson, 1999; Rigby *et al.*, 2001); altered hormonal responses (Troedsson, 1999; Rigby *et al.*, 2001); and, altered mucus production (Card, 2005; Causey, 2006). Other factors in multiparous mares include altered neuromuscular interactions (Rigby *et al.*, 2001), or impaired lymphatic drainage (Causey, 2006) due to partial dilation of the uterus (Troedsson, 1999) or caudo-ventral displacement of the uterus (LeBlanc *et al.*, 1998). All of these conditions enhance intrauterine inflammation and fluid accumulation (Troedsson, 1999; Guthjahr *et al.*, 2000).

The vulva, vestibule, vagina and cervix normally act as physical barriers protecting the uterus from external contamination (Katila, 1996; Troedsson, 1999; Rambags *et al.*, 2003) (Figure 1a). There is a higher predisposition towards PPBEM in mares with previous foaling injuries (Hurtgen, 2006), poor perineal conformation (Hurtgen, 2006), altered conformation of the vulva (Hemberg *et al.*, 2005) (Figure 1b) and incomplete closure or persistent relaxation of the vulvar lips (Rambags *et al.*, 2003; Hemberg *et al.*, 2005). Therefore, the above abnormalities can all affect barrier function, causing air, faeces and urine to enter the reproductive tract (Hurtgen, 2006). In addition, cervical incompetence has consequences for both barrier function and uterine clearance. It may include either insufficient relaxation during oestrus with impaired cervical drainage (Hurtgen, 2006; Pycock, 2006) or improper closure during dioestrus (Rambags *et al.*, 2003), predisposing to bacterial colonisation before breeding.

Physical clearance mechanisms in PPBEM

The equine uterus is strongly dependent on a physical clearance mechanism, which is based on ciliary beating and uterine contraction (Causey, 2007). An imbalance or breakdown of this sensitive system increases the risk of PPBEM in mares (Troedsson, 1999).

The equine endometrium consists of mucus secreting and ciliated cells (Causey, 2007). The cilia beat 13 times



Figure 1b: Altered conformation of the vulva. The labiae do not create a proper seal and the rectum is displaced cranially, allowing the vulva to be pulled dorsal to the ischiatic arch, causing constant faecal contamination of the vulva and vestibule.

per second and help to transport mucus, fluid, bacteria and other debris along the longitudinal folds of the endometrium and the cervix (Causey, 2007). However, dilated capillary spaces between the folds and damaged, scarred or atrophic folds disturb this precise clearance mechanism (Causey, 2007). Ulceration, degeneration and lack of cilia are suggested to have the same effect (Causey, 2007).

Mucus overlies, hydrates and lubricates the endometrium (Lagow *et al.*, 1999). It also prevents bacteria from binding to cell receptors (Lagow *et al.*, 1999; Causey, 2006). Water, ions, specific antibacterial proteins (including lactoferrin, lysozyme and immunoglobulins) and mucins are the main components of the mucus-gel (Howe *et al.*, 1999; Wiggins *et al.*, 2001; Olmsted *et al.*, 2003). Mucins are highly hydrated glycoproteins (Lagow *et al.*, 1999; Wiggins *et al.*, 2001). A change in the hydration of their polysaccharide chains is believed to disturb the viscosity and elasticity of the mucus (Causey, 2007). As a consequence, pathogens trapped in



Figure 2: The presence of free fluid in the uterine lumen (*) is diagnostic for the condition of PPBEM (Courtesy of Dr Christine Aurich, Vienna University).

the mucus and fluid are not cleared (Wiggins *et al.*, 2001, Olmsted *et al.*, 2003; Causey, 2007).

Smooth muscle cells form the inner circular and the outer longitudinal layer of the myometrium (Priedkalns and Leiser, 1998). It is hypothesised that contractile defects of the myometrium increase the susceptibility of mares to PPBEM (Nikolakopoulos and Watson, 1999; Rigby *et al.*, 2001). Troedsson *et al.* (1993) showed that the myometrial electrical activity, which was measured 20 hours after bacterial challenge, was increased in both resistant and susceptible mares. However, resistant mares showed a greater increase in frequency, intensity and duration of uterine electrical activity compared to susceptible mares (Troedsson *et al.*, 1993).

Diagnosis of susceptible mares

While PPBEM is easily diagnosed, its root causes are not always thoroughly investigated. A comprehensive assessment requires a detailed breeding history (Watson, 2000; LeBlanc, 2003). Any changes in perineal, vulvar or cervical conformation that predispose the mare to PPBEM should also be evaluated before breeding (Watson, 2000; LeBlanc, 2003; Hemberg *et al.*, 2005). It is very important to check that the cervix opens properly in oestrus and closes in dioestrus. Routine pre-breeding uterine swabs should be obtained from 'at-risk' mares, using double-guarded swabs. These minimise contamination with cervical, vaginal or perineal bacterial flora (Causey, 2006), offering the possibility of isolating organisms that are characteristic of susceptible mares, such as non-haemolytic *Escherichia coli* and β -haemolytic *Streptococcus* (Albihn *et al.*, 2003; Card, 2005; Nielsen, 2005). Bacteriology and cytology should always be conducted together, as the detection of PMNs together with potential pathogens is a much better indicator of the condition than bacteriology alone (Nielsen, 2005). Following this initial examination, confirmation of a diagnosis of PPBEM is achieved using transrectal ultrasound examination 24 to 48 hours after breeding. The presence of free fluid in the uterine lumen (more than 15

to 20mm in diameter) (Watson *et al.*, 2001; Barbacini *et al.*, 2003; Brinsko *et al.*, 2003) is diagnostic for the condition (Nikolakopoulos and Watson, 1999; Brinsko *et al.*, 2003; LeBlanc, 2003; Guevenc *et al.*, 2005) (Figure 2).

The earlier the diagnosis is made, the earlier the practitioner is able to start an effective treatment. This greatly enhances the chance of the mare carrying a foal to term. It is not uncommon that mares with a long history of normal fertility can spontaneously acquire PPBEM, giving the clinician no opportunity for prophylactic intervention (Watson, 2000).

Treatment options

The aim of the treatment is to completely clear fluid accumulation, contaminants and inflammatory products within 96 hours (Katila, 1996). This ensures that the embryo encounters a healthy endometrium at day five (Betteridge *et al.*, 1982), thus facilitating implantation (Card, 2005).

A single dose of oxytocin (10-20 IU, IM) is usually enough to clear uterine fluid less than 20mm in diameter (Pycock, 2006). If not, it should be repeated every four to six hours until the fluid is completely cleared (Pycock, 2006).

In mares with intra-uterine fluid accumulation of more than 20mm in diameter, treatment should consist of uterine lavage (Pycock, 2006). One to two litres of warm, sterile saline or a 0.05% povidone-iodine solution (5ml of a 10% povidone-iodine solution to each litre of balanced salt solution) (Brinsko, 2001) are infused via a large-bore equine embryo-flushing catheter until the recovered fluid is clear. This should be followed by administration of uterotonic substances such as oxytocin (Pycock, 2006); 10 IU pre-ovulatory and 25 IU post-ovulatory, IV or IM (Guthjahr *et al.*, 2000).

Another option is the administration of cloprostenol (a prostaglandin analogue; 250 µg IM daily, starting four hours after breeding) (LeBlanc, 2003) that clears the fluid more rapidly than PGF 2 α and has a longer duration of activity compared to oxytocin (Combs *et al.*, 1996). It is known that this drug has a negative effect on progesterone levels during early pregnancy (day two until day seven post-ovulation) when given throughout the periovulatory period until two days post-ovulation, but it does not decrease pregnancy rates, as the levels rise again at day seven and seem to be normal at day nine (Nie *et al.*, 2003).

The mare is re-examined 24 hours after initial treatment. If fluid is still present, treatment is repeated (Pycock, 2006). For susceptible mares, treatment should be timed with breeding and it should not be delayed until ovulation occurs (LeBlanc, 2003; Pycock, 2006). As long as the mare is in oestrus, the cervix remains open, allowing the practitioner to perform several flushes before ovulation, if necessary (Pycock, 2006). Treatment should be delayed for four hours after breeding (Rigby *et al.*, 1999). This allows enough time for the motile sperm to enter the uterine tube (Rigby *et al.*, 1999).

The day upon which oxytocin is administered also plays an important role in the contractility of the endometrium (Guthjahr *et al.*, 2000). It is suggested that mares that are

susceptible to post-breeding endometritis should have more time between breeding (24-48 hours before ovulation) and ovulation (Guthjahr, 2000; Paccamonti and Lyle, 2003).

Oxytocin treatment should be started in the pre-ovulatory period, as the response to oxytocin by the endometrium is higher when progesterone levels are low and oestrogen levels are high (Guthjahr *et al.*, 2000).

If oxytocin treatment is used after ovulation, the dose should be increased to achieve an effect (Guthjahr *et al.*, 2000; Paccamonti and Lyle, 2003). However, care has to be taken, as tetanic contractions can occur if more than 25 IU of oxytocin are administered, leading to retention of uterine fluid (Cadario *et al.*, 1999a). It is also suggested that an inflamed endometrium is more sensitive to oxytocin than a non-inflamed endometrium (Veronesi *et al.*, 2006).

It is very important that the treatment is based on the individual mare, as standard treatment may not be effective in all cases (Pycock, 2006).

Optimal breeding management

Optimising the breeding management of the mare is the most important aspect in reducing the susceptibility of the mare for post-breeding endometritis, but it is also an aspect that is often underestimated. Prevention is always better than cure.

Choosing the right time for breeding or inducing ovulation (2,500 IU of hCG when the follicle has a diameter more than 35mm) (Samper, 2001; Pycock, 2006) reduces the need for more than one insemination during oestrus (Rambags *et al.*, 2003; Pycock, 2006). Thus the spermatozoa are not exposed to an inflammatory uterine environment (Alghamdi *et al.*, 2001; Troedsson *et al.*, 2001).

Early breeding enhances the chance of accumulated fluid being expelled before the cervix starts to close rapidly after ovulation. In addition, the natural immune defence mechanisms of the endometrium are more pronounced during oestrus than in dioestrus (Katila, 1996; Pycock, 2006). With regard to breeding hygiene, bandaging the mare's tail and cleaning the vulva and perineal area with clean water help to minimise contamination during cover (Pycock, 2006).

AI with fresh or cooled semen is another means by which uterine inflammation can be reduced (but not eliminated), as exogenous bacterial contamination is limited (Pycock, 2006). It is very important to know that old mares bred with frozen semen are at a higher risk of developing PPBEM, as seminal plasma is reduced by the process of cryopreservation (Vidament *et al.*, 1997; Troedsson *et al.*, 2001). Therefore, its suppressive effect on post-breeding endometritis is lost (Troedsson *et al.*, 2001).

New trends in insemination, for example the use of sex-sorted (frozen-thawed) semen, require low sperm dose insemination techniques to achieve pregnancy (Sieme *et al.*, 2003; Guevenc *et al.*, 2005; Lyle and Ferrer, 2005). The uterotubal junction (UTJ) is the sperm reservoir in the mare (Lyle and Ferrer, 2005). Therefore, transrectally-, transendoscopically- or ultrasonographically-guided deep intrauterine horn insemination with a flexible catheter, onto

or close to the UTJ papilla, is becoming more and more popular (Sieme *et al.*, 2003; Guevenc *et al.*, 2005; Lyle and Ferrer, 2005). Approximately one to 25 x10⁶ progressively motile spermatozoa in volumes between 20 and 1,000µl are needed (Lyle and Ferrer, 2005). This low number of spermatozoa is preferred when inseminating into the uterine horn ipsilateral to the dominant pre-ovulatory follicle to avoid increased inflammation in normal mares (Guevenc *et al.*, 2005).

However, it should be borne in mind that these methods require a very skilled and experienced inseminator and that they seem to result in lower pregnancy rates in problem mares (Sieme *et al.*, 2003).

Correction of anatomical defects, for example by Caslick's vulvoplasty operation, can protect and prevent the reproductive tract from constant external contamination, air aspiration (Causey, 2006) and ascending inflammation (Pycock, 2006).

Conclusion

Much research has been performed over the last few decades to determine the reasons for this multi-factorial condition in mares. There are also successful and accepted treatment programmes, which help improve pregnancy rates by completely clearing fluid early after breeding. However, more effective and rapid prognostic and diagnostic tests are required for improved management of PPBEM.

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