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A review of a practitioner's perspective on endometrial edema

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Summary

Determination of uterine health and proximity to ovulation is paramount in equine reproductive management. Observation and recording of the changes in uterine edema is a useful tool to maximize reproductive management. This paper describes the uterine edema scoring system used by the author and its interpretation, as well as signs of abnormal edema and some of the therapeutic options that are currently used to address abnormal and/or pathological edema.

Keywords: Reproduction, endometrial edema, hyper-edema, Equine, Reproductive management

Eine Übersicht über das uterine Ödem aus der Sicht des Pferdepraktikers

Die Bestimmung der uterinen Gesundheit und des Ovulationszeitpunktes ist von höchster Bedeutung im equinen Reproduktionsmanagement. Das Beobachten und Dokumentieren der Veränderungen des uterinen Ödems liefert in diesem Zusammenhang sehr wertvolle Informationen. Dieser Artikel stellt das vom Autor eingesetzte Schema zur Auswertung des uterinen Ödems und dessen Interpretationen vor. Des Weiteren werden Anzeichen für abnorme Ödeme beschrieben sowie einige therapeutische Möglichkeiten aufgezeigt, die im Falle eines abnormen bzw. pathologischen Ödems genutzt werden können.

Schlüsselwörter: Reproduktion, endometriales Ödem, übermäßiges Ödem, Pferd, Reproduktionsmanagement

Introduction

Ultrasonographic evaluation of the uterus is done in order to determine pathological or physiological conditions and uterine contents (*McKinnon* et al. 1988). Because the mare is a seasonal polyestric animal there are physiological changes that must be taken into account when examining the mare. The cervix, uterus and ovaries change significantly between anestrus, transition and regular cyclicity (estrus and diestrus) (*Daels* and *Hughes* 1993).

Once the mare has had the first ovulation of the year, the interovulatory interval is on the average 20-22 days. Ovulation is preceded by a follicular phase which typically lasts 5-7 days during which the mare shows behavioural estrus, and followed by a luteal phase which lasts 14 to 16 days and the mare is not receptive to the stallion for natural mating (*Bergfeldt 2008). However, unlike other domestic animals the* mare has an LH peak after ovulation and often displays strong signs of heat for up to 48 hours after ovulation. Although mares can be bred as far as 6 days prior to ovulation with acceptable pregnancy results, to maximize their fertility, mares should be mated within 48 hours prior and up to 6 hours post-ovulation A single mating as many as five or six days before ovulation with a fertile stallion will often result in pregnancy, but pregnancy rates increase when mares are bred closer to ovulation (*Woods* et al. 1990). Therefore accurate prediction of ovulation becomes a critical component of breeding management in order to maximize the efficiency of a breeding operation and ultimately the pregnancy rates (*Squires* et al. 1988). Current systems to determine the timing of breeding rely on several of the following: teasing with a stallion, cervical relaxation determined by rectal palpation or vaginal speculum exam, presence of a large size follicle detected by rectal palpation and ultrasonography, appearance of the follicle on ultrasound exam, timing from treatment with an ovulation inducing agent and the presence and pattern uterine edema (*Pelehach* et al. 2002, *Ginther* and *Pierson* 1994, *Watson* et al. 2003)

Because mare behaviour is unreliable and current practices in the equine artificial insemination industry make it difficult to use a stallion to determine behavioural estrus, teasing is an undependable method to predict the ideal time for insemination. Follicular growth during the luteal phase in a major secondary wave can often result in the presence of a large follicle during diestrus; therefore ultrasonographic evidence of a follicle alone is not indicative of estrus. (*Bergfeldt* 2008)

This paper describes the uterine edema scoring system used by the author and its interpretation, as well as signs of abnormal edema and therapies that are currently used to address abnormal or pathological edema.

Normal pattern of uterine edema

The mare under the influence of estrogen will have increase edema of the reproductive tract. This includes mild hyperaemia of the vulvar lips and vagina with a concomitant relaxation of the vaginal vault and cervix. In addition there is a typical estrogenic appearance of the uterus that has been descri-

bed as a "cart wheel pattern". The appearance and disappearance of endometrial edema during the estrus period is a progressive phenomenon that is directly related to the presence of estrogen and basal levels of progesterone in a normal mare (*Pelehach* et al.2002, *Pycock* et al. 1995, *Hayes* et al. 1985, *Plata-Madrid* et al. 1994, *Griffin* and *Ginther* 1991).

Table 1 Average degree of edema (n=253) according to the stage of the cycle and day of estrus graded on a subjective scale from 0-5. Different superscripts denote differences ($p<0.05$) between grades of edema.
Durchschnittlicher Grad des Ödems (n=253) in Bezug auf den Zyklusstand (Tage des Östrus) basierend auf einer subjektiven Skala von 1 bis 5. Unterschiedliche hochgestellte Indizes bezeichnen die statistischen Unterschiede (p<0,005) zwischen den Ödemgraden.

Stage of Cycle	Degree of edema
Diestrus	0.3 ± 0.9^{a}
Estrus Day 1	1.2 ± 1.7^{b}
Day 2	1.8 ± 1.6^{b}
Day 3	3.9 ± 1.3^{c}
Day 4	2.3 ± 1.8^{bd}
Day 5	1.5 ± 1.5^{b}
Day 6	1.0 ± 1.5^{b}
Day 7	0.2 ± 0.7^{a}

Table 2 Rate of dissipation of uterine edema in mares (n=86) after treatment with 2.2 mg of deslorelin acetate (Ovuplant™). Different superscripts denote differences ($p<0.05$) between examination times. All mares were treated when they were considered to have maximal degree of edema.
Rate des Rückganges des uterinen Ödems bei Stuten (n=86) nach Applikation von 2,2 mg Deslorelinazetat (Ovuplant ™). Unterschiedliche hochgestellte Indizes bezeichnen die statistischen Unterschiede (p<0,005) zwischen den Untersuchungszeitpunkten. Alle Stuten wurden dann behandelt, wenn angenommen wurde, dass das Ödem sein Maximum erreicht hat.

Hours after Ovuplant™	Degree of Edema
0	4.5 ± 0.5^{a}
12	4.1 ± 0.4^{a}
18	$3.6 \pm 1.2^{a,b}$
24	$2.6 \pm 1.8^{b,c}$
30	1.5 ± 1.7^{d}
36	1.1 ± 1.4^{d}
42	0.8 ± 2.1^{d}
48	$0.5 \pm 2.7^{d,e}$
60	0.2 ± 1.6^{e}

In the authors practice a numeric subjective score from 0-5 to grade the degree of endometrial edema is used with 0 being no edema and 5 being maximal edema. A typical mare would have 0 edema during diestrus, and 4 for maximal degree of normal edema. Uterine edema score of 5 for what the author considers an abnormal edema and will be referred to as "hyper-edema" (*Samper* 2008). The analysis of the appearance and disappearance of uterine edema of 253 mares using a 0-5 subjective score (*Samper* 1997) resemble a Gaussian distribution with a progressive increase of uterine edema in the initial days of the follicular phase and a dissipation or disappearance as the mare approaches ovulation. However the variation in uterine edema is significant between mares (Table 1). The dissipation of the edema after treatment of mares (n=86) with the GnRH analogue deslorelin acetate (Ovuplant®) was not significant during the first 12-18 hrs post treatment and then disappeared progressively as the mare approached ovulation. Again there was a significant amount of variation in the rate of dissipation between mares. (Table 2)

Normal uterine edema (Figure 1a - e)

Having a consistent scoring system to grade endometrial edema is paramount in able to use the information to manage the reproductive cycle of the mare. On or at around day 15 of diestrus, the non-pregnant mare releases prostaglandin from the endometrium which causes luteolysis. Progesterone levels reach basal levels between 12 and 24 hrs of this release (*Bragg-Weaver* et al. 2002).

Uterine edema grade 0- (UE0)
A uterus with no edema is characterized by a very homogenous echotexture and the presence of an active corpus luteum.

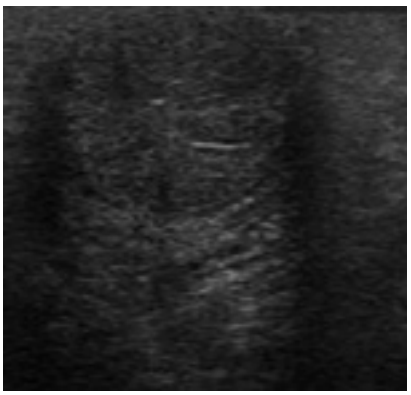

Fig.1a Uterine edema grade zero (UE 0) Typical endometrial echotexture of a progesterone dominated uterus. Note the homogeneity of the uterus.
Grad 0 (UE 0), typische Echotextur des Endometriums bei progesteronbeeinflusstem Uterus. Auffällige Homogenität des Uterus.

Uterine edema grade 1- (UE1)
A mare that is just starting to come in heat will be characterized by a moderately soft cervix at palpation, the presence of a 25-35 mm follicle depending on breed and size of the mare. However UE1 can also be present on a mare that is very close to ovulation. The presence of a large softening follicle with uterine folds of a uterus with UE1 can be difficult to identify and unless there is a record of a previous examination it could be undetectable. However the difference in echotexture with UE0 is noticeable but no individual folds are identifiable.

Uterine edema grade 2- (UE2)
As shown in Figure 1C, this demarcates the first real sign of uterine edema in the mare and most often will be detected at the cervix and is visualized ultrasonographically as a fish-bone appearance. Follicles can be 35+ mm and often you can easily identify some of the endometrial folds on ultraso-

nography. UE2 can also be present as the mare approaches ovulation with a follicle greater than 40 mm in diameter and a very soft cervix.

Fig. 1b (UE 1) Although there is no visualization of individual endometrial folds there is a distinct heterogeneity compared to the image in figure A.
Grad 1 (UE 1) Trotz Fehlens einzelner endometrialer Falten fällt eine deutliche heterogene Echogenität des Gewebes im Vergleich zu Grad 0 auf.

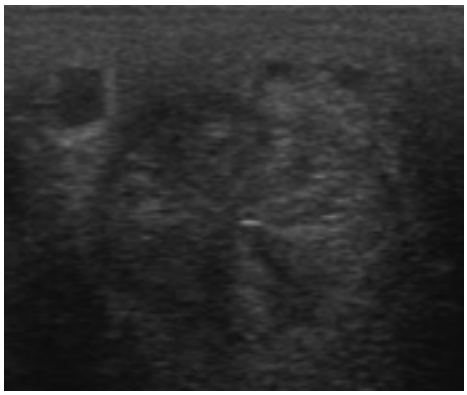

Fig. 1c (UE 2) This edema grade is characterized by the appearance of distinct endometrial folds although not visible through out the uterus.
Grad 2 (UE 2) Deutliche Faltenbildung des Endometriums jedoch nicht über den gesamten Uterus ausgedehnt.

Uterine edema grade 3- (UE3)
Grade 3 edema is easily identifiable and a true "cart wheel" pattern is observable. The echotexture of the uterus is completely heterogeneous. The folds are identifiable individually and are slightly thicker at the base compared to the image of the grade 2 folds. Follicles are 38-40 mm or more and the endometrial folds can be easily observed throughout the uterus. Mares with UE3 are good candidates for treatment with ovulatory inducing agents, with ovulation occurring between 36 and 48 hrs post-treatment.

Uterine edema grade 4- (UE4)
This is the maximal grade of edema considered normal with the presence of a hard 40 + mm dominant follicle. The folds are thickened and possibly hyperplastic resulting in a typical increase of the width of the endometrial folds. Ultrasonographically the folds have hyperechoic borders and hypo-echoic center. However the ultrasonographic uterine architecture of the cart wheel is still maintained.

At this point in a normal mare the uterine edema will start to decrease as the mare approaches ovulation reaching its nadir immediately prior or post ovulation. Follicle size will remain

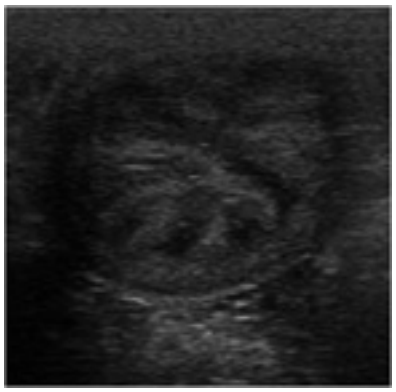

Fig. 1d (UE 3) Cart wheel pattern with folds visible through the uterus. However the folds are slightly hypoechoic in the center.
Grad 3 (UE 3) Radspeichenstruktur mit über den gesamten Uterus ausgedehnter Faltenbildung des Endometriums. Endometriale Falten mit geringgradig hypoechogenen Zentren.

Fig. 1e (UE 4) Folds are prominent with a distinct hyperechoic border and an increase in the endometrial fold thickness.
Grad 4 (UE 4) Prominierende Falten mit Hyperechogenität der Grenzbereiche und erhöhter Wanddicke.

the same (40-55) as the edema decreases or can decrease slightly as it changes shape during its migration towards the ovulation fossa.

In most normal mares the variation in endometrial edema from estrus to diestrus is very pronounced, (ranging from 1-4), However not all mares will have this pronounced variation in uterine edema, but, well over 90% of the mares will have detectable uterine edema when in estrus. Mares that do not display uterine edema while progesterone levels are basal should be considered abnormal. Even though the mare has a heavy inflammatory reaction shortly after insemination due to the presence of sperm (post-breeding induced endometritis), this reaction is seldom detected as an increase in the degree of endometrial edema in the normal mare at 24 hrs post-breeding.

Abnormal uterine edema (Figure 2)

There are several instances when the veterinarian performing and ultrasonographic examination of the uterus should

suspect the possibility of uterine problems when assessing the degree of edema. These include but are not limited to increase of endometrial edema post breeding, persistence of heavy edema post ovulation, presence of endometrial edema at 14-15 days post ovulation and lack of endometrial edema.

Uterine edema grade-5 (UE-5)
As shown in Figure 2, this type of edema has several characteristics such as: a) Abnormally thick endometrial folds making the uterus loose the normal architecture of the cart wheel pattern hence the term Hyper-edema, b) Folds are very thick with bright borders and mottled centers, c) Often there is the presence of detectable amount of uterine fluid in the body or in the cervical lumen.

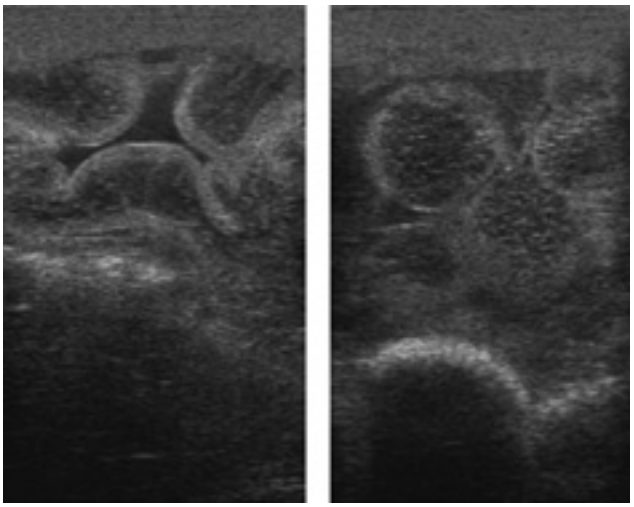

Fig. 2 Uterine edema grade 5 (UE 5) This endometrial grade is referred as "Hyper-edema" and is characterized by a disruption of the normal uterine architecture. Folds are significantly thickened with hyperechoic borders and hypoechoic centers. Free fluid can often be detected in some areas of the uterus particularly in the uterine body and the cervix.
Endometriales Ödem Grad 5 (UE 5). Dieser Grad wird auch als "Hyper-ödem" bezeichnet und erscheint als Auflösung der normalen uterinen Gewebsarchitektur. Die endometrialen Falten fallen durch signifikant verdickte Wände, hyperechogene Grenzflächen und hypoechogene Zentren auf. Freie Flüssigkeit im Uterus wird häufig insbesondere an den Prädilektionsstellen Uteruskörper und Zervix beobachtet.

In a recent study by *Samper* (2007) the pregnancy rate per cycle was significantly higher (14%) for mares that had uterine edema 1, 2 or 3 when ovulation was detected compared to mares that ovulated with edema scores of 4 or 5. Furthermore, the presence of uterine fluid at the time of ovulation was significantly lower ($p<0.05$) for mares with edema grades 1 and 2 at the time of ovulation (12.6 and 24.4%), compared to mares ovulating with edema 3 (32.4%) edema 4 (38.8%) or edema 5 (58.4%). All mares that were considered to have hyper–edema, or mares whose edema did not decrease at the time of ovulation were cultured and an endometrial cytology performed. Of these mares 64.9% had a positive culture and/or cytology. The seasonal pregnancy rate for mares that displayed hyper-edema was 73.8% but the average number of cycles per pregnancy was increased compared to the mares in the other groups.

Dealing with edema

In most normal mares the variation in endometrial edema from estrus to diestrus is very pronounced, (ranging from 0-4). Although not all mares will have this pronounced variation in uterine edema, more than 90% of the mares will have detectable uterine edema when in estrus. Mares that do not display uterine edema while progesterone levels are basal and estrogen is high should be considered abnormal (*Pelehach* et al. 2002, *Pycock* et al. 1995).

Even though the mare has a physiological heavy inflammatory reaction, known as post-breeding induced endometritis, shortly after insemination due to the presence of sperm (*Troedsson* et al. 2005), this reaction is seldom detected as an increase in the degree of endometrial edema in the normal mare at 24 to 48 hrs post-breeding.

Uterine edema can be indicative of uterine pathology when there is one or more of the following:

- Presence of obvious endometrial edema and a large follicle 14-15 days post-ovulation
- Presence of hyper-edema during the normal estrus period
- Failure to reduce the edema as the mare approaches ovulation and the presence of marked uterine edema 24 hours post ovulation
- Significant increase in the degree of uterine edema 12-24 hours post-breeding
- Lack of uterine edema during the estrus period (*McKinnon* et al. 1988, *Pelehach* et al. 2002, *Squires* et al.1988).

In a study by *Bucca* et al. (2008), mares that had histories of accumulating fluid or had persistence of fluid post breeding were treated with 50 mgs of dexamethasone at the time of service. The use of dexamethasone on these mares resulted in a significantly higher pregnancy rated on the treated cycle compared to non-treated control mares. A strong clinical impression by the author suggests that the use of 20 mgs of dexamethasone i.m. or i.v. 4-6 hrs post breeding will significantly reduce the degree of endometrial edema of mares with a significant increase or lack of reduction of edema post-breeding. However these mares also benefit from the use of uterine lavage and an ecbolic agent.

Conclusion

Interpretation of endometrial edema requires a good quality ultrasound and evaluation of the mare on a regular basis during the late diestrus and the estrus period until ovulation is detected. If used critically and consistently, the pattern of uterine edema can aid the practitioner in determining uterine health and guide the veterinarian for possible diagnostic or therapeutic procedures that may help increase the fertility of mares. Following the pattern of endometrial edema is a key tool to help veterinarians manage mares reproductively and can help in giving a prognosis of pregnancy in a given breeding cycle.

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