Reproductive management of the transitional mare

The mare is a seasonally polyoestrous long-day breeder with a physiological breeding season lasting from April–October in the Northern Hemisphere. The hypothalamic-pituitary-gonadal axis in the mare is subject to a circannual endogenous rhythm that is primarily regulated by day length. Increasing ambient photoperiod in the spring alters the pattern of melatonin secretion. The resulting stimulation of hypothalamic gonadotropin-releasing hormone secretion triggers pituitary follicular stimulating hormone release and follicular growth. Exposure of mares in deep anoestrus to a stimulatory photoperiod remains the most successful method of advancing the first ovulation of the season. The most commonly used lighting regimen is providing a fixed length of 15–16 hours of light exposure and 8–9 hours of dark, with a minimum light intensity in a stable of 100-lux (100–200 watt incandescent bulb). Other methods include using an additional 2.5 hours of light beginning at sunset and a pulse lighting system, providing 1 hour of light, 9.5–10.5 hours after the onset of darkness, during the photosensitive phase. Alternatively, the Equilume™ light masks provide a unilateral LED light source emitting 50 lux of blue-light directly to the eye during the hours after dusk (until 11 pm). Mares that have not been maintained under lights, or that have been exposed to ineffective light therapy, may require therapeutic hormonal intervention to advance the onset of the first ovulation of the season. Many hormone protocols involving progestins, GnRH, dopamine agonists and recombinant luteinising hormone/follicle stimulating hormone have been studied with variable results. Therapy is typically more effective when started either in late transitional mares or following a period of stimulatory artificial photoperiod. https://doi.org/10.12968/ukve.2020.4.2.42

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The mare is a seasonally polyoestrous long-day breeder, with a physiological breeding season lasting from April–October in the Northern Hemisphere. Evolution has ensured that foals are born at times of favourable environmental and nutritional conditions, thus maximising their chances of survival.

The hypothalamic-pituitary-gonadal axis in the mare is subject to a circannual endogenous rhythm that is primarily regulated by day length (Ginther, 1992). Light signals detected by the retina are processed by photosensitive retinal ganglion cells. The retino-hypothalamic tract sends signals to the suprachiasmatic nucleus in the hypothalamus, which is connected to the pineal gland via the superior cervical ganglia (Murphy, 2019). Increasing ambient photoperiod in the spring inhibits the release of the neurotransmitter norepinephrine, which subsequently inhibits melatonin secretion from the pineal gland. Removal of the inhibitory action of melatonin on the mare's reproductive axis results in stimulation of hypothalamic gonadotropin releasing hormone (GnRH) secretion, triggering pituitary follicle stimulating hormone (FSH) release and follicular growth (Donadeu and Watson, 2007). Initially, follicles are steriodogenically incompetent, with positive feedback on luteinising hormone (LH) secretion only occurring when a dominant follicle releases sufficient oestrogen to cause an LH surge, resulting in the first ovulation of the year and the end of the transition period (Davis and Sharp, 1991). The first ovulation of the season is reported on average to be 7 April +/- 9.1 days in horses and 7 May +/- 21.1 days in pony mares (Sharp, 1983).

Historically in the Thoroughbred industry, there has been a commercial emphasis on early-born foals, as it is thought that they have growth and maturity advantages over their later-born contemporaries, and higher earning potential (Langlois and Blouin, 1998). Owners therefore want to start breeding mares in mid-February, when there is a seasonal absence of follicular development. Breeding barren mares at the beginning of the season also reduces the pressure on stallions when foaling mares are ready to be bred later in the season. Early initiation of cyclicity additionally will increase the number of oestrous cycles in which mares can be used in embryo transfer programmes during the season.

The most common method of inducing early follicular development and ovulation is advancing the onset of the 'transition period' between winter anoestrus and spring cyclicity by providing an artificial photoperiod; however, alternative or concurrent therapeutic intervention may be required.

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Photoperiod

Exposure of mares in deep anoestrus to a stimulatory photoperiod remains the most common method of advancing the first ovulation of the season. The duration from onset of adequate light exposure to ovulation is approximately 60 days, although there is considerable variation between individual mares (Guillaume et al, 2000). It is important to realize that an artificial photoperiod does not shorten the transition period but rather initiates the transition from anoestrus to cyclicity sooner in the year. Both the mare's photoperiodic history and the potential to become refractory to treatment if maintained under constant lighting conditions should be considered, and as such it is important to precede light treatment with a period of short days. The peak sensitivity to transitions from short to long days in the mare occurs around the beginning of December. No further advancement of the first ovulation of the season was reported when photoperiod treatment was initiated on 1 November, while a delay to first ovulation was reported when light therapy was initiated on 1 January (Scraba and Ginther, 1985). Light treatment is therefore typically started at the beginning of December in Europe and after Thanksgiving in the USA.

At temperate latitudes, within a given day each continuous night period should not exceed 9 hours in duration, in order to limit melatonin secretion.

The most commonly used lighting regimen is providing a fixed length of 15–16 hours of light exposure and 8–9 hours of dark, with a minimum light intensity in a stable of 100-lux (100–200 watt incandescent bulb) (Guillaume et al, 2000). Other methods include using an additional 2.5 hours of light beginning at sunset, and a pulse lighting system providing 1 hour of light, 9.5–10.5 hours after the onset of darkness, during the photosensitive phase, which results in an immediate decrease in melatonin concentrations when the lights are turned on, followed by increased levels when the lights are switched off (McCue et al, 2007).

Alternatively, the Equilume™ (Equilume, Naas, Ireland) light masks provide a unilateral LED light source emitting 50 lux of blue light directly to the eye during the hours after dusk, until 11 pm, ensuring a 15-16 hour daylength (*Figure 1*). In a controlled study, 59 Thoroughbred mares were split into three groups and from 1 December were either: housed indoors under a lighting regime (Group 1); housed outside with a light mask (Group 2); or housed outside with no additional lighting (Group 3). The mares were examined every 2 weeks between 20 November and 10 February for evidence of oestrous cyclicity (follicles >20 mm diameter detected in conjunction with serum progesterone >1 ng/mL and confirmation of ovulation by transrectal ultrasound examination). On 10 February, 87.5% of mares in Group 1, 80% mares in Group 2 and 21% of mares in Group 3 showed oestrous cyclicity, suggesting the low-intensity blue light masks to be an effective alternative to maintaining mares indoors under lights for advancing the breeding season (Walsh et al, 2014).

More recently, a customised LED stable lighting system (*Figure 2*) has been developed for horses that better mimics the spectrums and qualities of environmental light, comprising timed polychromatic white light by day that peaks in the blue light spectrum; low intensity red light at night; and gradual transitions at dawn and dusk. Robust circadian rhythmicity was observed in gene

Figure 1. The Equilume™ light mask provides light to the eye while kept outdoors. (Image courtesy of Equilume)

Figure 2. For housed mares, stable lighting can be used to provide a longer daylength; the Equilume Stable Light shown here is an LED light designed to mimic environmental light better than a traditional incandescent bulb. (Image courtesy of Equilume)

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expression of hair follicle cells collected from horses housed under the customised LED system, versus expression patterns that tended to flat-line in horses under traditional lighting (Collery et al, 2018).

When deciding on the most appropriate lighting regime for a stud farm, it is important to consider other factors that have been shown to influence the time to first ovulation in the spring, such as temperature, nutrition, body condition score and proximity to a stallion (Wespi et al, 2014). In harsh environmental conditions, mares may benefit from being housed inside under lights, where they can be rugged and fed additional concentrates as required, whereas in moderate conditions, the benefits of pasture turn out and additional exercise may make an Equilume™ light mask the treatment of choice.

Pharmacological manipulation

Mares that have not been maintained under lights, or that have failed to respond optimally to light therapy, may require hormonal intervention to advance the onset of the first ovulation of the season (*Figure 3*). Many hormone protocols have been studied, with variable results. Therapy is typically more effective when started either in late-transitional mares or following a period of stimulatory artificial photoperiod.

Dopamine receptor antagonists

The dopamine receptor antagonists sulpiride and domperidone have been shown to increase circulating levels of prolactin and stimulate follicular growth and/or ovulation during spring transition. The exact mechanism of action of dopamine in the mare is unclear, but it is thought to act directly on the ovary through the D2 receptor protein, to inhibit follicular growth — hence the stimulatory effect of an antagonist. The effects of dopamine antagonists are variable between studies and between individual mares, which may be due to differences in time of administration (anoestrus vs. transition); dose; duration of treatment; and pre-treatment photoperiod exposure (Tibary, 2011). In the author's experience, dopamine antagonists are most effective in mares in mid-to-late transition with evidence of uterine oedema and follicles >20 mm in diameter.

Progestins

Progestins such as altrenogest and progesterone in oil have no consistent effect on follicular development and gonadotrophin secretion patterns in mares in early transition. Progestins will, however, suppress oestrous cycles during transition and synchronise the first ovulation of the year, in mares in mid-to-late transition and those exposed previously to an artificial photoperiod. Protocols include 10–14 days of altrenogest (Regumate, MSD Animal Health) (0.044 mg/kg PO SID) or long-acting bio-release altrenogest (Bova UK). When a single injection of long-acting progesterone was administered to mares in late transition (20–25 mm follicles), ovulation rates were significantly improved compared to controls, with 83% of treated mares ovulating between 10–24 days post treatment, compared to 25% of control mares (Staempfli et al, 2011). However, this protocol had no effect on mares in early or mid transition (follicles <20 mm diameter).

Vaginal inserts such as the progesterone-releasing intravaginal device PRID® DELTA (Ceva Animal Health) have been shown to be very effective in late transitional mares. Insertion for 7–10 days during transition (20–25 mm follicles) resulted in follicular growth and ovulation within 4 days of device removal, with 95.2% of treated mares being bred within the first 21 days of the season, compared to 42.6% of controls (Hanlon and Firth, 2012). A transient vaginitis

Figure 3. A selection of treatments used in the management of the transitional mare.

Table 1. Therapeutic agents used to manage the transition period in mares

Medication	Brand name	Administration
GnRH agonists		
Buserelin	Receptal (MSD Animal Health)	12.5 µg IM or SC, BID
Deslorelin	Compounded (Bova Specials UK)	125 µm IM BID
Gonadorelin	Fertagyl (MSD Animal Health)	250–500 µg IM BID or QID
Goserelin	Zoludex (Astra-Zenica UK)	½–1/3 of 3.6 mg implant SC once
Progestins		
Altrenogest	Regumate (MSD Animal Health)	0.044 mg/kg PO SID
Altrenogest in oil	Compounded (Bova Specials UK)	150 mg IM
Progesterone (vaginal insert)	PRID® DELTA (Ceva Animal Health)	1.9 g of progesterone
Dopamine antagonists		
Domperidone	Human tablets or compounded (Bova Specials UK)	1.1 mg/kg PO SID
Sulpride	Human tablets or compounded (Bova Specials UK)	1.0 mg/kg PO SID or BID

Adapted from McCue et al (2007).
IM: intramuscular, PO: oral, SC: subcutaneous
Note: The prescribing cascade must be followed if deciding to use products not licensed for horses in the UK.

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KEY POINTS

- Providing an artificial photoperiod remains the most common method of advancing the first ovulation of the year. At temperate latitudes the period of darkness should not exceed 9 hours, to limit melatonin secretion.
- There are various methods of providing an artificial photoperiod but the Equilume Stable Light most closely mimics natural environmental light and in addition to its effect on the circadian rhythm has been shown to have other health benefits.
- Various hormone treatments have been used to manipulate the transition period, with recombinant follicle stimulation hormone/recombinant luteinising hormone being the most promising, especially in mares in deep anoestrus. These products unfortunately are not currently available commercially, but may well be the future treatment of choice.
- With appropriate case selection, intravaginal progesterone devices offer a convenient, economical and reliable method for managing transition in mares on commercial stud farms. While less cost effective, slow-release implants of gonadotropin releasing hormone analogues are reliable, convenient and have minimal side effects.
- When determining the most appropriate option for transition management it is important to consider both the mare and client, as owner compliance is vital for success.

is commonly reported with the use of these implants, but appears to have little impact on subsequent fertility (Newcombe, 2002). Reports have also suggested that a percentage of mares may experience some discomfort following insertion of a PRID® DELTA. WIth appropriate case selection, intravaginal progesterone devices offer a convenient, economical and reliable method for managing transitional mares on commercial stud farms.

GnRH agonists

Both native GnRH and GnRH agonists, such as buserelin, deslorelin, gonadorelin and goserelin, have been used to increase gonadotropin release and hence follicular growth and ovulation with variable results. Ovulation rate and number of treatment days have been shown to correlate to follicular size at the onset of treatment and to depth of anoestrus. Mares in deep anoestrus are at risk of returning to anoestrus following a GnRH-induced ovulation, whereas those in transition are more likely to continue to cycle (McCue et al, 1991). A recent study treated Thoroughbred mares with 12.5 μg buserelin IM BID following a 2–week standard 16-hour lighting protocol, and compared the number of treatment days, ovulation status, pregnancy and return to oestrus. The average length of treatment was 10.42 days; 94% of transitional mares and 65% of anoestrous mares ovulated following buserelin treatment, with an overall pregnancy rate of 72%. Of the mares that did not become pregnant, 100% continued to cycle following treatment. This study supports the use of buserelin to stimulate folliculogenesis in combination with a short lighting program in both anoestrous and transitional mares (Wolfsdorf et al, 2018. Slow-release implants of GnRH analogues (Zoldex®) are reliable and do not require repeated adminstration (single implant) and as such are favorable, but may be most costly than other options.

FSH

Recombinant FSH(reFSH), purified equine FSH and equine pituitary extract have been shown experimentally to stimulate follicular growth and ovulation in mares deep in anoestrus. In one study, over 70% of recombinant eFSH treated mares showed follicular growth and ovulation within 5–10 days, compared to 0% of control mares. Starting on 21 January this meant that treated mares had their first ovulation of the year within approximately 10 days, compared to around 75 days in the control group. With the addition of recombinant LH (reLH), mares that did not conceive continued to cycle on the reFSH/reLH protocol, compared to those on reFSH alone, which returned to anoestrous (Loud et al, 2014). Unfortunately these products are not currently commercially available, but if they were to come on the market they would likely be very popular, particulary since unlike most other products they are effective even in mares in deep anoestrous.

Other factors to consider

Various other factors have been shown to augment the effects of the photoperiodic changes, including environmental conditions, nutrition, age and breed. A 10-year study in Australia showed that onset of ovarian activity was closely related to minimum and maximum environmental temperatures in spring, and that cold weather could slow follicular growth (Guerin and Wang, 1994). Various nutrition studies have discussed the stimulatory effect on follicular development and time to first ovulation in mares introduced to lush grass (Carnevale et al, 1997), feeding high quality protein and a positive energy balance (Van Niekerk and Van Niekerk, 1997). Conversely, reduced levels of insulin-like growth factor (IGF-1), a local growth factor essential for folliculogenesis, have been found in mares fed a diet deficient in energy and protein (Salazar-Ortiz et al, 2011). Current recommendations are that mares should enter the breeding season with a BCS >5 (on the scale 1 to 9, Henneke et al, 1983) and a body fat content >15%. Spatial proximity to a stallion has also been shown to significantly shorten the time to the first ovulation of the season (Wespi et al, 2014). Age may alter ovarian activity during the transition period, with older mares having been shown to have less follicular activity during this time (Carnevale et al, 1997). Failure to ovulate in the postpartum period is most likely attributed to seasonal or nutritional affects rather than as a direct effect of lactation. It is advised that pregnant mares due to foal early in the season are maintained under artificial lighting for the last 2–3 months of pregnancy. This has been shown to shorten their gestation length by up to 10 days, and to increase their chances of a foal heat ovulation and ongoing cyclicity postpartum (Hodge et al, 1982). EQ

Conclusions

Advancing the first ovulation of the year remains common practice, and providing an artificial photoperiod is still currently the most

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successful way to do so, but since this will not shorten the process of vernal transition in the mare, it is important to allow adequate time for mares to benefit. Mares that have not been maintained under an artificial photoperiod, or have not responded optimally to treatment, may require further hormonal manipulation. There are various advantages and disadvantages to the treatment options discussed. It is important to select a protocol on evidence-based medicine but also one that is cost-effective and convenient, to ensure client compliance.

Conflict of interest: none.

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